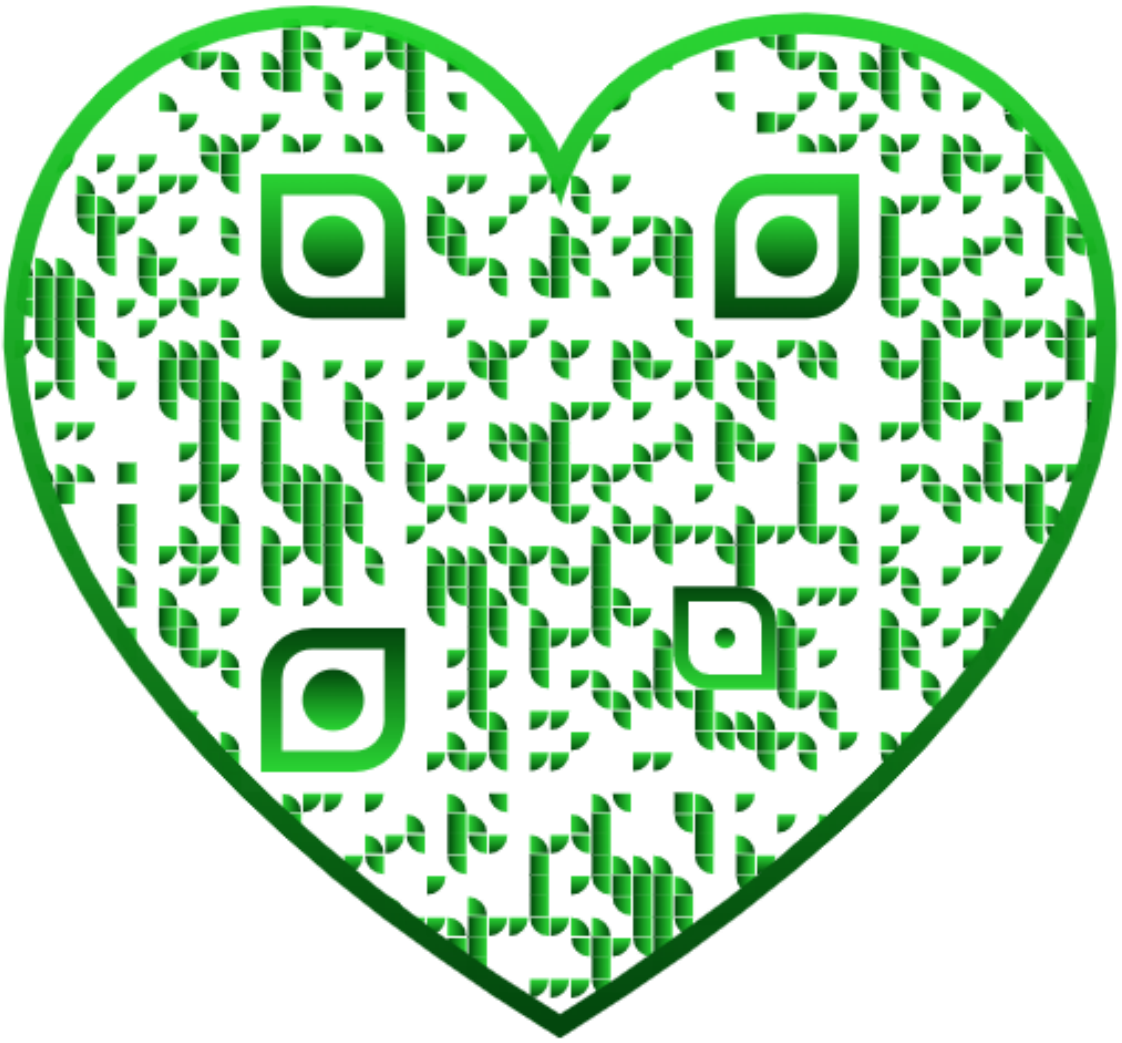
Basic Unit operations in Industrial Pharmacy

- Size reduction
- Size separation
- Mixing
- Drying
- Filtration and clarification
- Crystallization



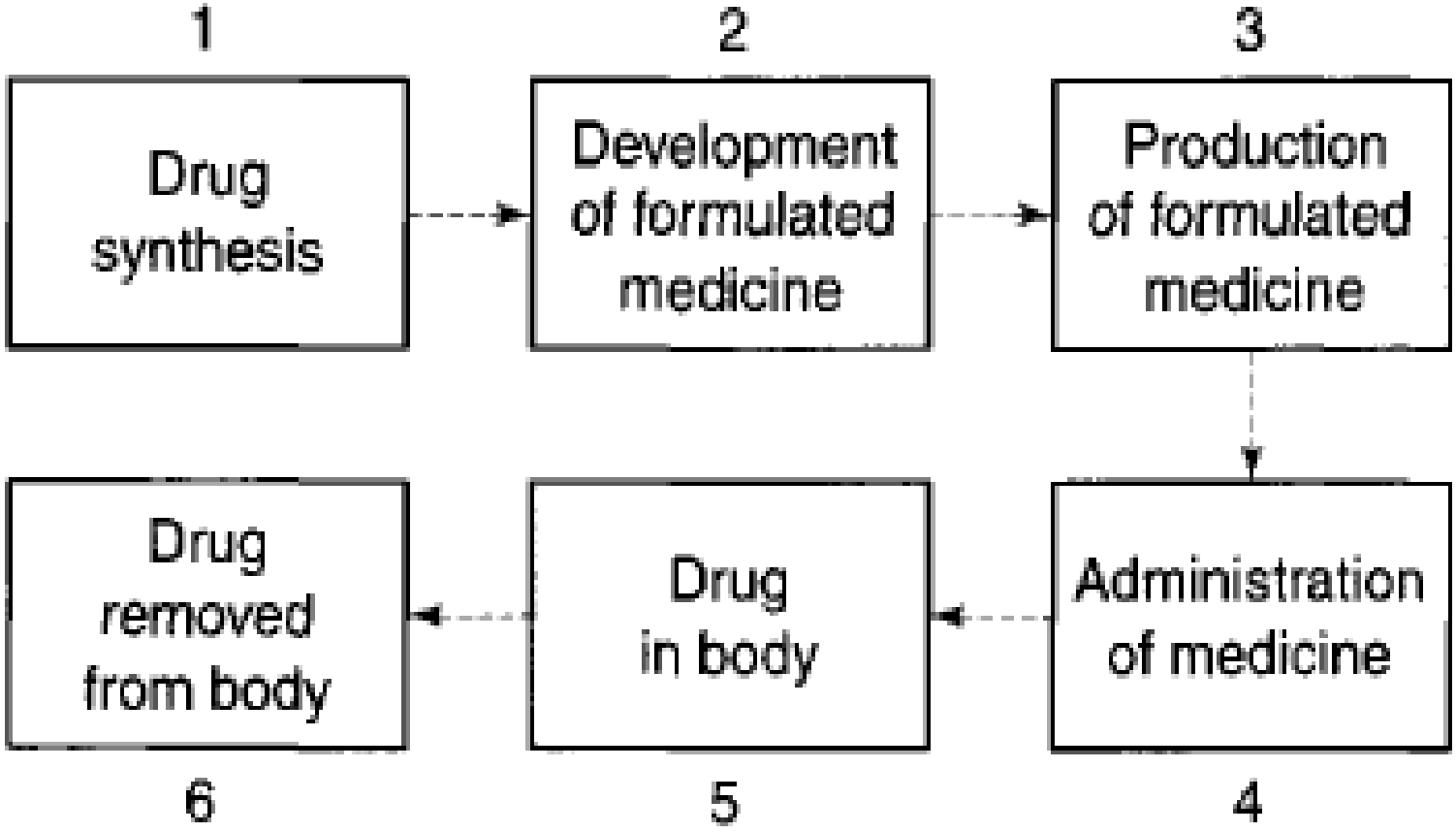
Introduction

- In any industry a unit operation is a basic step in a process
- A process may require many unit operations to obtain the desired product from the starting materials,
  - E.g. In tablet processing: mixing, milling, drying and sifting
- It is convenient to break down the processes for the manufacture of pharmaceutical products into unit operations.

1. Particle Size Reduction

- The dimensions of particulate solids are important in achieving optimum production of efficacious medicines,

- Particle size influences the subsequent physical performance of the medicine and the pharmacological performance of the drug,


1
2
3
Drug synthesis
Development of formulated medicine
Production of formulated medicine
Drug removed from body
Drug in body
Administration of medicine
6
5
4

...

- Pharmaceutical applications of size reduction
  - Increases the SA of drugs which helps in rapid dissolution,
  - Increases the therapeutic effectiveness of certain drug,
  - Facilitates extraction or leaching of crude drugs.
  - Shortens time of dissolutions of solids.
  - Facilitate drying of wet masses
  - Increase powder flow ability.
  - Facilitate uniform mixing or blending of several solid ingredients
  - Reduce the bulk of a material.
  - Improve stability of emulsion

...

Material properties and Size reduction

1) Crack propagation and Toughness

- Size reduction is carried out by a process of crack propagation,
  - localized stresses produce strains in the particles which are large enough to cause bond rupture and thus propagate the crack
  - Once initiated, the crack tip propagates at a velocity approaching 40% of the speed of sound in the solid, and brittle fracture occurs

...

- Some materials can resist fracture at much larger stresses,
- Such tougher materials can undergo plastic flow,
  - Which allows strain energy relaxation without crack propagation,
  - When plastic flow occurs, atoms or molecules slip over one another,
  - Such type of deformation requires energy,

...

2) Surface hardness

- The hardness of a material can be described by its position in Mohs' scale
  - Mohs' scale is a table of hardness of materials
  - At the top of which is diamond with Mohs' hardness >7
  - At the bottom of the table with Mohs' hardness <3 is talc

...

- Harder materials are generally more difficult to comminute and can lead to abrasive wear of metal mill parts,
- Conversely, materials with a large elastic component, such as rubber, are extremely soft yet difficult to size reduce,
- Hard (e.g. metals) vs. Soft (e.g. rubber) vs. Waxy (e.g. stearic acid) vs. Sticky (e.g. gums) materials ??

...

3) Abrasiveness

- It is a property of hard material
- It may limit the type of machinery that can be used because it may worn the grinding mill

...

4) Stickiness

- It may cause difficulty in size reduction,
- May **adhere** to the grinding surfaces, or the meshes of screens may become chocked.
- Example: Grinding of gummy or resinous materials.

...

5) Slipperiness

- It is the reverse of stickiness
- A material acts as a lubricant and lowers the efficiency of the grinding surfaces.

...

6) Moisture content

- In general, a moisture content below 5% is suitable for dry grinding and greater than 50% if wet grinding is to be carried out.

...

Energy requirements of Size reduction process

- Only a very small amount of the energy put into a comminution operation actually effects size reduction and other lost in different ways
  - Elastic deformation of particles
  - Plastic deformation of particles without fracture
  - Deformation to initiate cracks that cause fracture
  - Deformation of metal machine parts
  - Inter-particle friction and particle-machine wall friction
  - Heat, sound and vibration

...

- Theories relating energy input to the degree of size reduction produced:
  - Rittinger's hypothesis
    - The energy used in a size-reduction process is proportional to the new surface area produced,
  - Kick's theory
    - The energy used in fracturing a set of particles of equivalent shape is proportional to the ratio of the change in size

- Bond's theory
  - The energy used in crack propagation is proportional to the new crack length produced, which is often related to the change in particle dimensions
- Walker relationship
  - A generalized differential form of the energy-size relationship which can be shown to link the theories of Rittinger and Kick, and in some cases that of Bond

...

Size reduction methods

1) Cutting method

- Size range: 100 - 100000 µm
- Principle of operation:
  - Cutter mill is used consisting of a series of knives attached to a horizontal rotor
  - Rotor knives move against stationary knives attached to the mill casing
  - A screen is fitted in the base of the mill casing

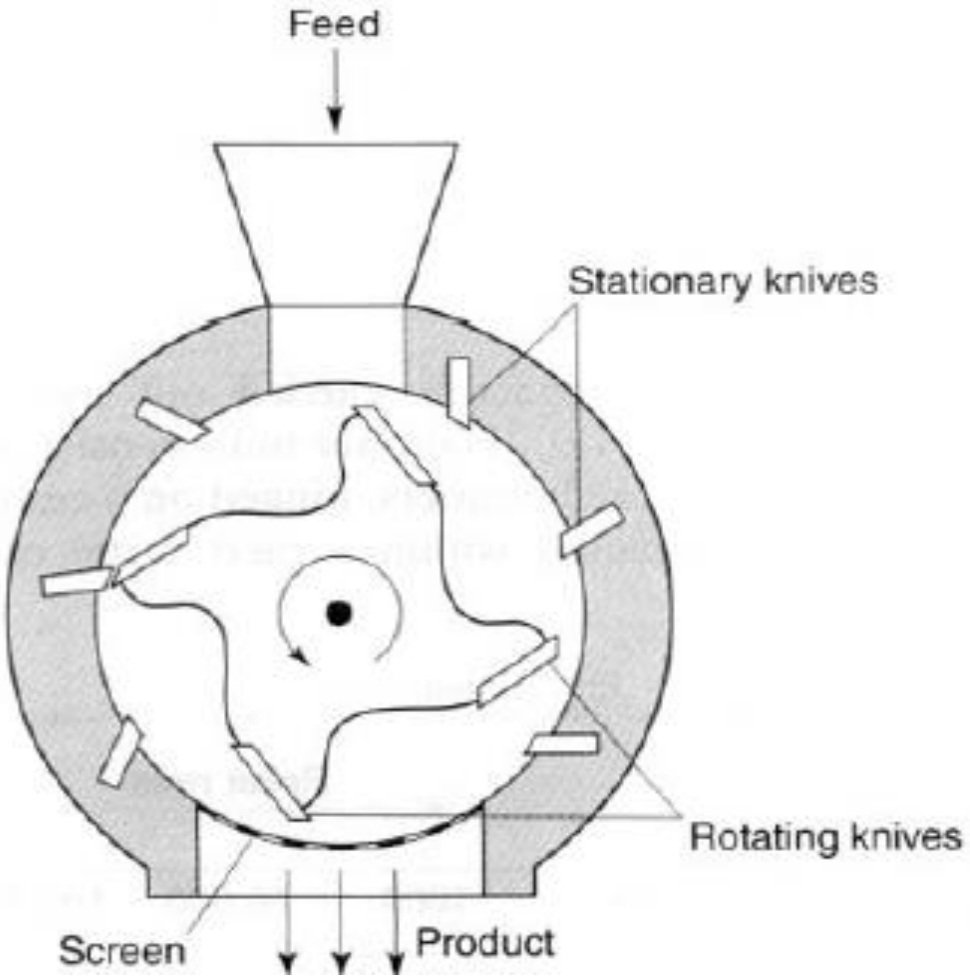


Fig. Cutter mill

...

2) Compression method

- Size reduction range: 50 μm to 100 mm
- Principle of operation:
  - End-runner mill ~ a weighted pestle is turned by the friction of material passing beneath it as the mortar rotates under power
  - Edge-runner mill ~ has the pestle equivalent mounted horizontally and rotating against a bed of powder, so that size reduction occurs by attrition as well as compression

- Roller mill ~ one of the rolls is driven directly while the second is rotated by friction as material is drawn through the gap between the rolls

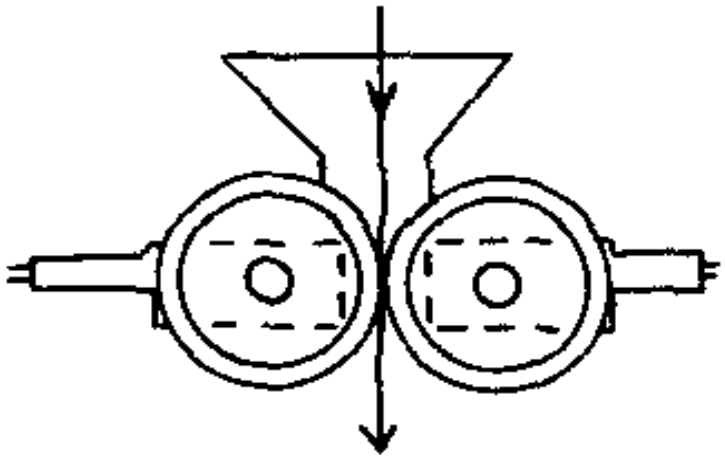


Fig. Roller mill

- Advantages:
  - Energy efficient
  - Uniform particle-size distribution
  - Little noise and dust generation
- Disadvantages:
  - Little or no effect on fiber
  - Particles tend to be irregular in shape and dimension
  - May have high initial cost (depends on system design)
  - When required, maintenance can be expensive

...

3) Impact method

- Size range: 1µ to 1mm (vibration mills), 50µm to <10 mm (hammer mills)
- Principle of operation:
  - Hammer mills – consist of a series of hammers hinged on a central shaft which swing out radially from the rotating central shaft.
  - Vibration mills – filled ~80% total volume with porcelain or steel balls which vibrates during milling and size reduction occurs by repeated impaction.

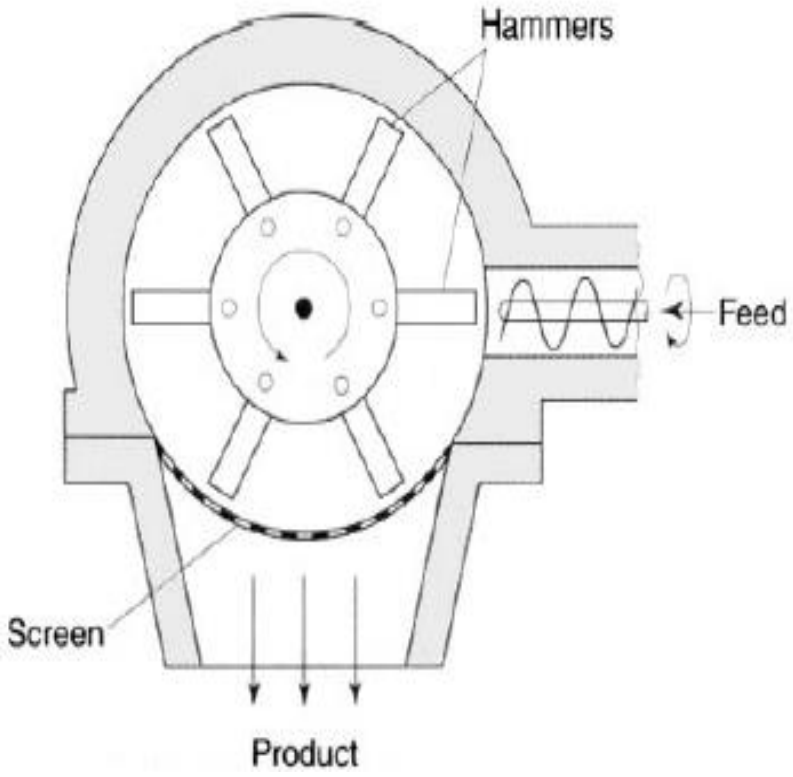


Fig. Hammer mill

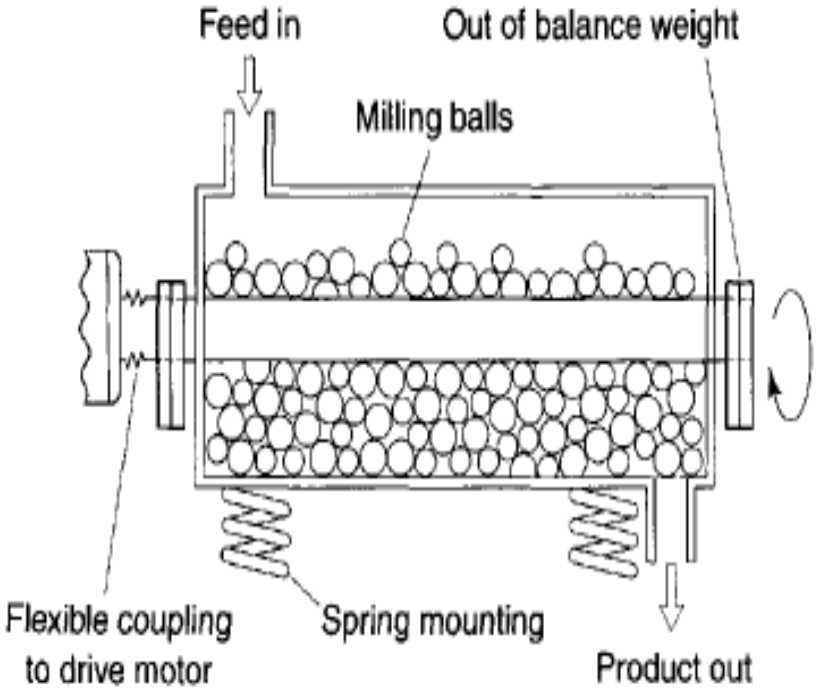


Fig. Vibration mill

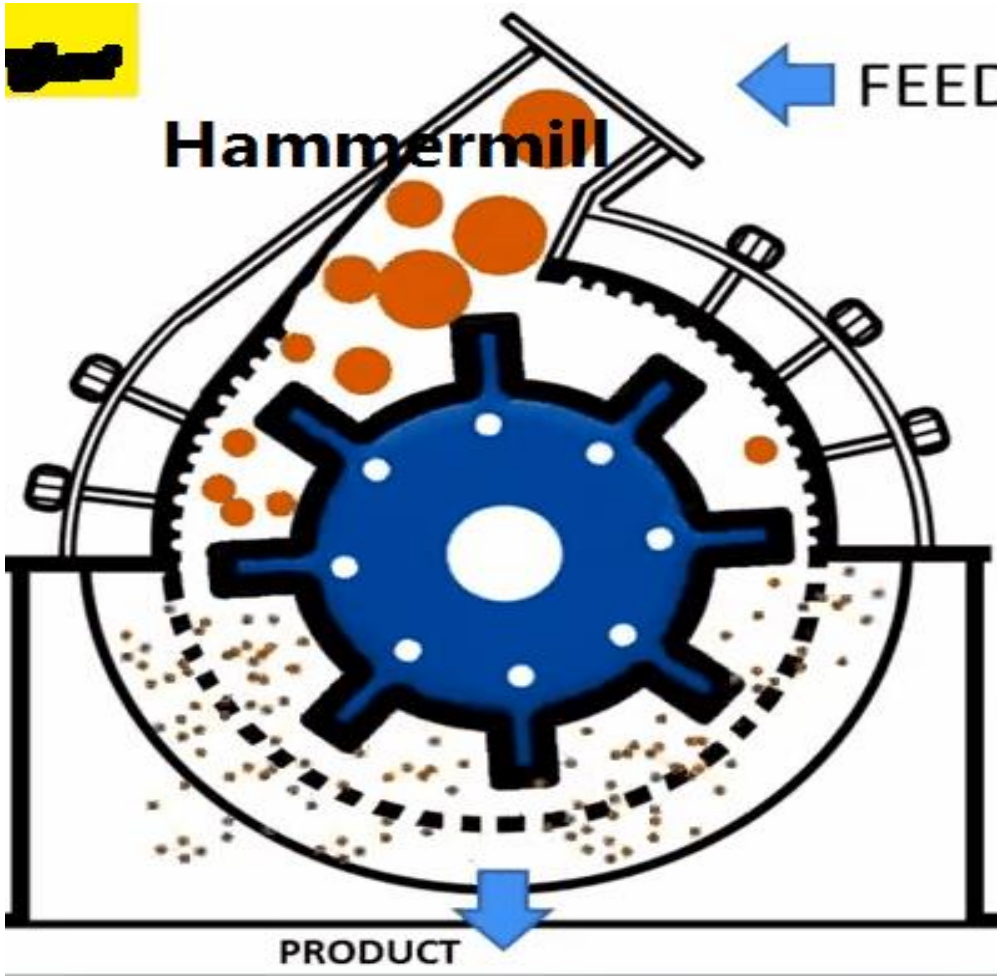


Fig. Hammer mill operation

- Advantages
  - It is rapid in action.
  - Size can be controlled by rotor speed; hammer type; size and shape of mesh.
  - Operation is continuous
  - No surfaces move against each other, so that there is little contamination.

- Disadvantages
  - The process generates heat that may affect thermolabile materials.
  - The mill may be chocked, resulting in decreased efficiency or even damage.
  - Because of the high speed of operation, the hammer mill is susceptible to damage by foreign objects such as metal in the feed.

...

4) Attrition method

- Size range: 1 μm to 100 μm
- Principle of operation
  - Roller mills ~ use the principle of attrition to produce size reduction of solids in suspensions, pastes or ointments,
  - Mortar and Pestle ~ for small scale

...

5) Combined impact and Attrition methods

- Size ranges: Ball mills (1 to 100 μm), Fluidized energy mills (1 to 10 mm), and Pin mills (10 μm to 10mm)

- Principle of operation

  - Ball mills ~ consist of a hollow cylinder (up to 3m diameter) mounted such that it can be rotated on its horizontal longitudinal axis, and filled with balls occupying 30-50% of the total volume

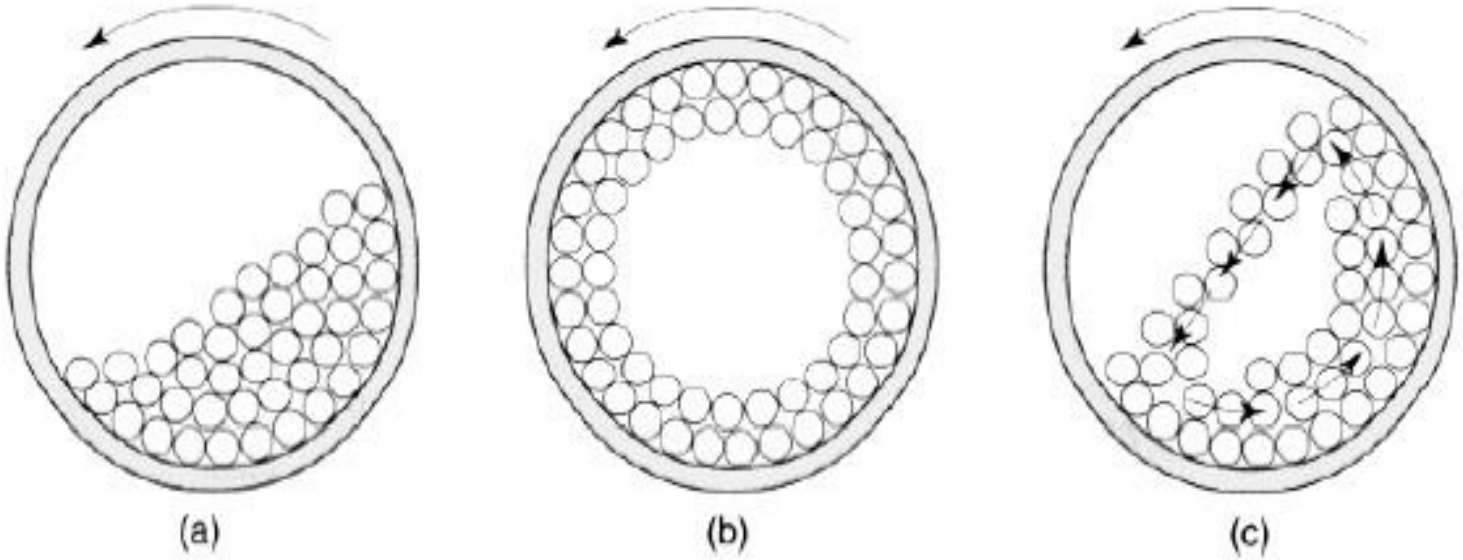


Fig. Operation of a Ball mill

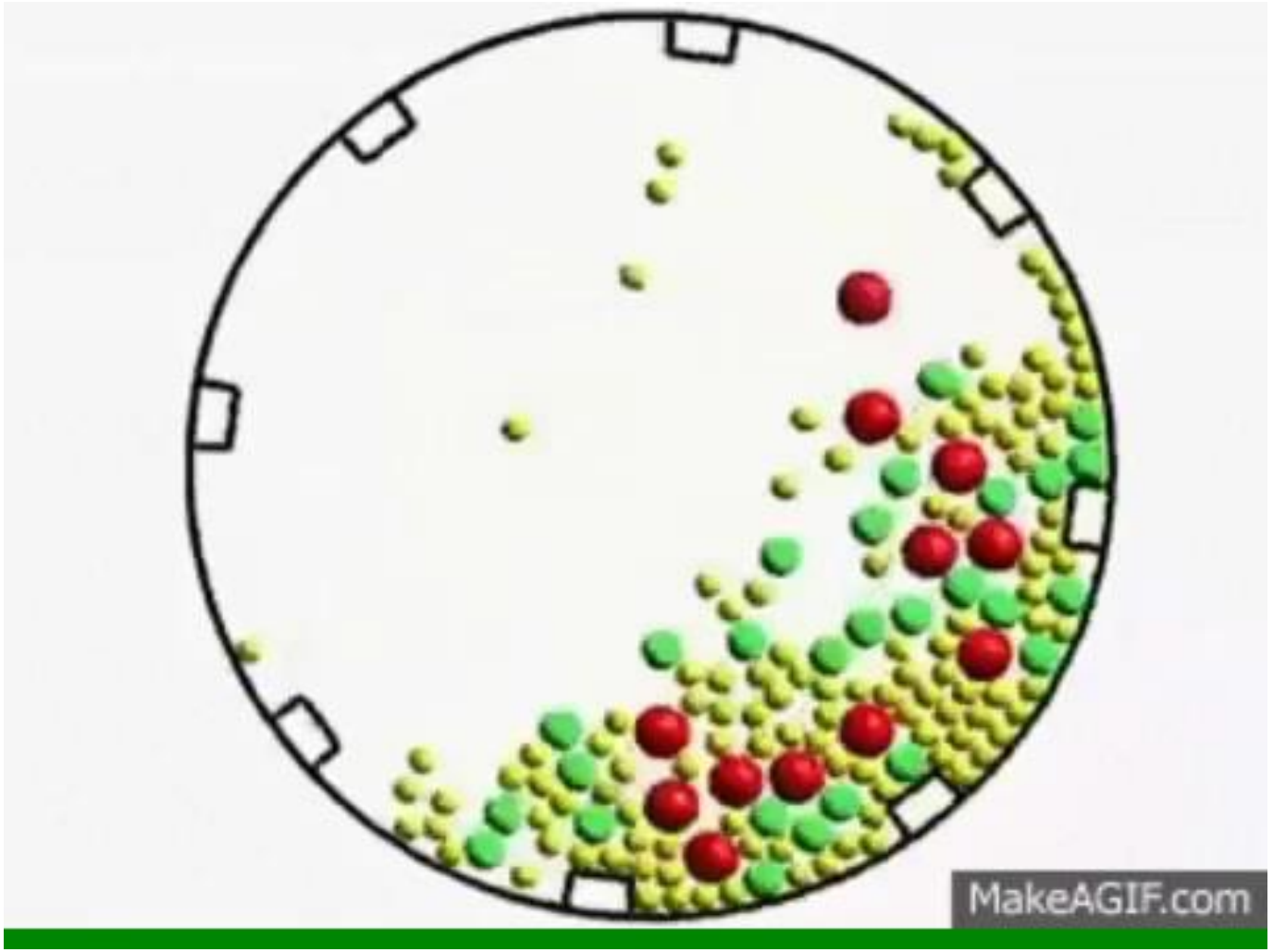


Fig. Operation of a Ball mill

- Fluid energy or jet mill ~ consists of a hollow toroid which has a diameter of 20 to 200 mm,
  - A fluid, usually air, is injected as a high-pressure jet through nozzles at the bottom of the loop
  - The high velocity of the air gives rise to zones of turbulence into which solid particles are fed.
  - The high kinetic energy of the air causes the particles to impact with other particles

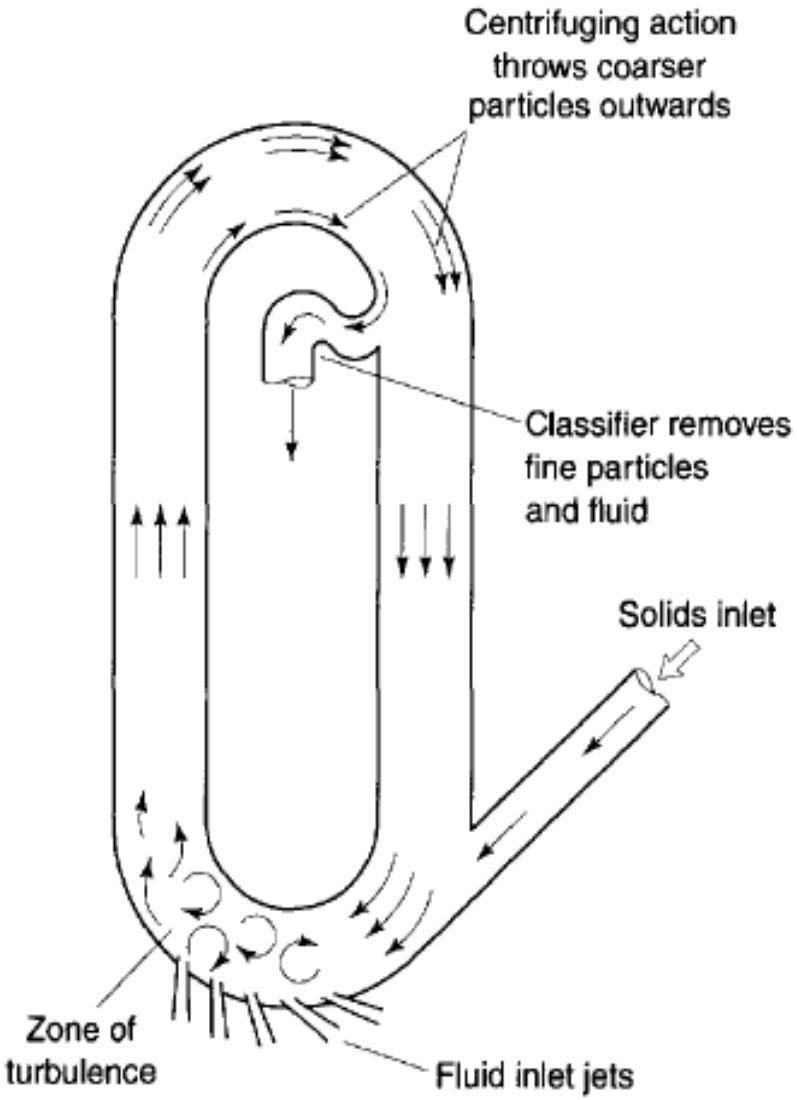


Fig. Fluidized energy or Jet mill

- Pin mills ~ act by producing particle impact and attrition
  - Two discs with closely spaced pins rotate against one another at high speeds.
  - Particle-size reduction occurs by impaction with the pins and by attrition between pins

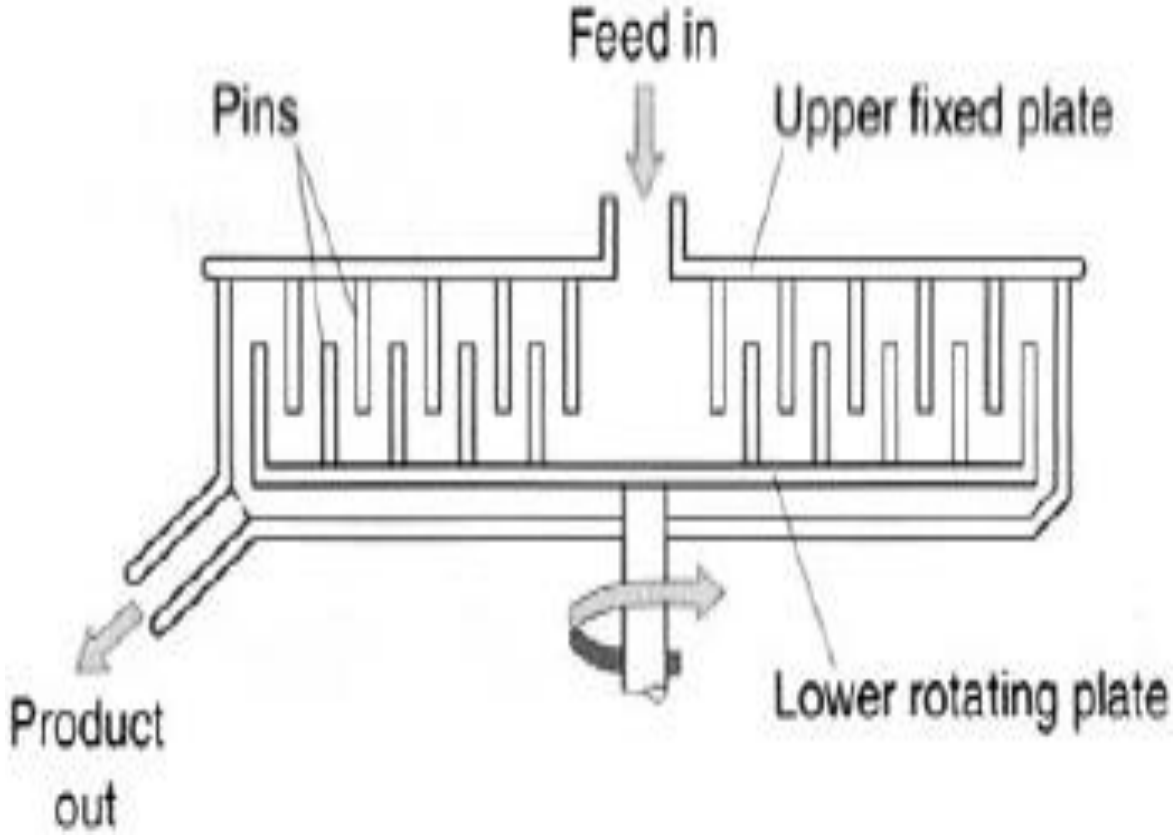

Feed in
Pins
Upper fixed plate
Product
out
Lower rotating plate

Fig. Pin mill

...

- Selection of particle size reduction method

Degree of size reduction	Typical methods	Examples
Large pieces	Cutter or compression mills	Rhubarb
Coarse powders	Impact mills	Liquorice cascara
Fine powders	Combined impact and attrition mills	Rhumbarb, Belladonna
Very fine powders	Fluid energy mills	Vitamins, Antibiotics

...

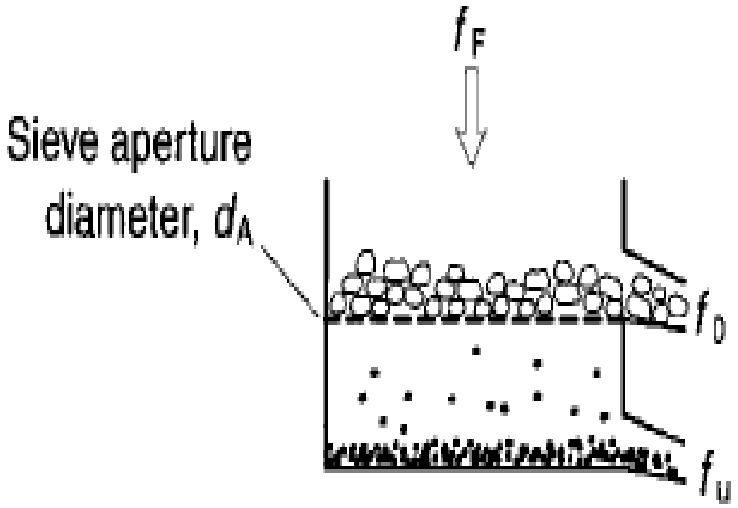
- Further reading assignment
  - Advantages and limitations of each the size reduction methods/techniques.
  - Practical applications of each method/techniques of size reduction.

2. Particle Size Separation

- Objective:
  - To classify powders into separate particle size ranges,
  - And, a given particle size range is available for separate handling or subsequent processing.

...

- Size-separation Efficiency:
  - Determined as a function of the effectiveness of a given process in separating particles into oversize and undersize fractions,



...

- In a continuous size-separation process, the production of oversize and undersize powder streams:

$$f_F = f_O + f_U$$

- If the separation process is 100% efficient, then:
  - all oversize material will end up in the oversize product stream, and
  - all undersize material will end up in the undersize product stream.

...

- And, if we consider the oversize material,
  - From the total feed, a certain proportion of true oversize material, δf,
  - From this:
    - will contain a fraction, δ0, being oversize particles, and
    - will contain a fraction, δU, being undersize material

...

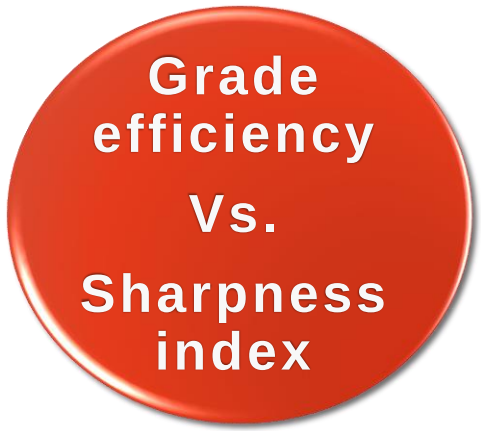
- Then, the efficiency of the separation of oversize material, can be determined by:

$$E_o = \frac{f_o \times \delta_o}{f_F \times \delta_F}$$

- Similarly, the efficiency of the separation of undersize material, can be determined by:

$$E_u = \frac{f_u(1-\delta_u)}{f_F(1-\delta_F)}$$

- And, total efficiency: $E_t = E_u \times E_o$



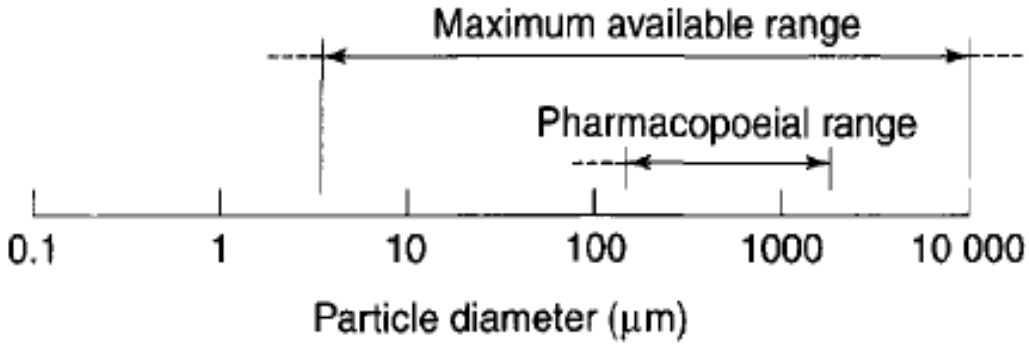
...

Size-separation Methods

1) Size separation by Sieving

- Using this method for size separation over size analysis ??
  - Stainless steel meshes for size separation where as for size analysis are brass and bronze,
  - The sieves used for size separation are often larger in area than those used for size analysis.

- Size range:


Maximum available range
Pharmacopoeial range
0.1
1
10
100
1000
10 000
Particle diameter (μm)

- Principles of operation

A) Agitation

- Oscillation ~ electrically induced
- Vibration ~ mechanically induced, or
- Gyration ~ sieves are subject to move out-of balance flywheel

B) Brushing

- A brush is used to re-orientate particles on the surface of a sieve and prevent apertures becoming blocked,
- A single brush can be rotated about the midpoint of a circular sieve,
- For large-scale processing, a horizontal cylindrical sieve, is employed, with a spiral brush rotating about its longitudinal axis

C) Centrifugal methods

- Particles are thrown outwards on to a vertical cylindrical sieve under the action of a high-speed rotor inside the cylinder,
- The current of air created by the rotor movement also assists in sieving,
- Especially, where very fine powders are being processed

...

- Grading of powder (USP powder grade):
  - **Very coarse (No. 8):** All particles pass through No. 8 sieve and not more than 20% pass through No. 60 sieve.
  - **Coarse (No. 20):** All particles pass through a No. 20 sieve and not more than 40% pass through a No. 60 sieve.
  - **Moderately coarse (No. 40):** All particles pass through a No. 40 sieve and not more than 40% pass through a No. 80 sieve.
  - **Fine (No. 60):** All particles pass through a No. 60 sieve and not more than 40% pass through a No.100 sieve.
  - **Very fine (No. 80):** All particles pass through a No. 80 sieve. There is no limit to greater fineness.

SIEVE NUMBER	SIEVE OPENING
2.0	9.50 mm
3.5	5.60 mm
4.0	4.75 mm
8.0	2.36 mm
10.0	2.00 mm
20.0	850.00 µm
30.0	600.00 µm
40.0	425.00 µm
50.0	300.00 µm
60.0	250.00 µm
70.0	212.00 µm
80.0	180.00 µm
100.0	150.00 µm
120.0	125.00 µm
200.0	75.00 µm
230.0	63.00 µm
270.0	53.00 µm
325.0	45.00 µm
400.0	38.00 µm

...

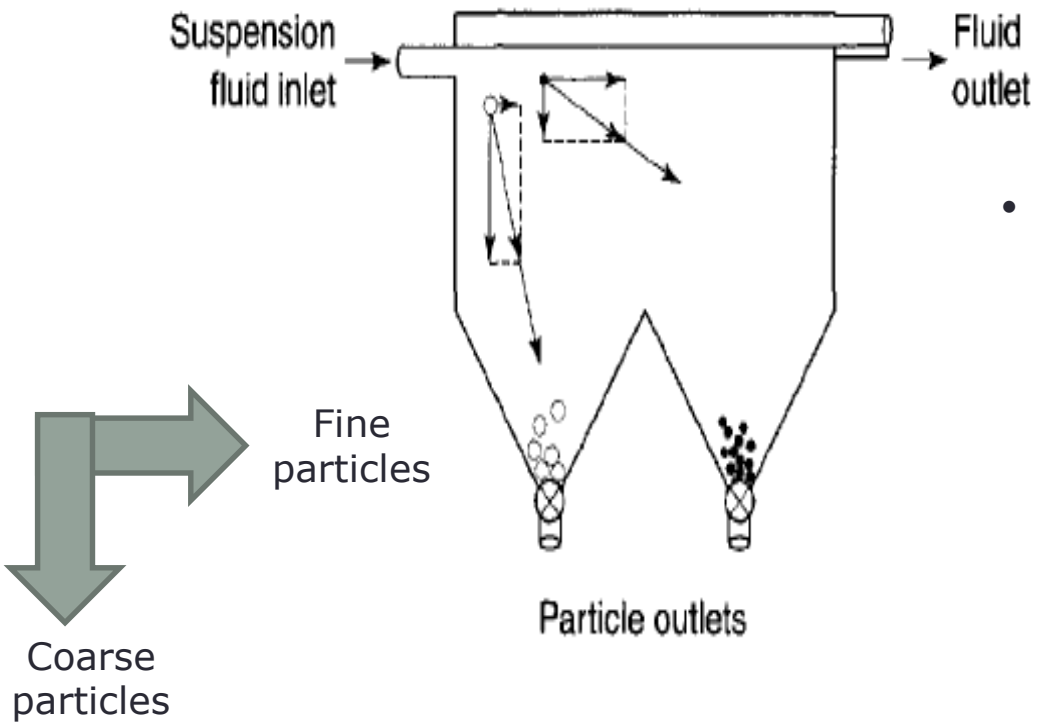
2) Size separation by Fluid classification

A) Sedimentation methods (Size range: 0.1 – 5µm and 5 - 100µm)

- Principles of operation:
  - Particles sediment by virtue of their particle size,
  - Rate of settling and particle size can be related according to Stokes‘ equations (and Reynolds' number ~ 0.2?),
  - E.g. a chamber containing a suspension of solid particles in a liquid (usually water),
  - A particular size range can be collected (how?).

...

- An alternative technique is to use a continuous settling chamber so that particles in suspension enter a shallow container



- Driving forces:
  - Horizontal component of particle velocity which is equal to the suspension fluid velocity, and
  - Vertical component which corresponds to Stokes' settling velocity

...

- In order to increase the driving force of sedimentation,
  - Centrifugal methods can be used to separate particles of different sizes in the sub-micrometre region,
  - Simple cylindrical centrifuges can be used to remove single size cuts from a fluid stream,
  - But, where separation is required over a wider number of size ranges multiple-chamber centrifuges can be used.

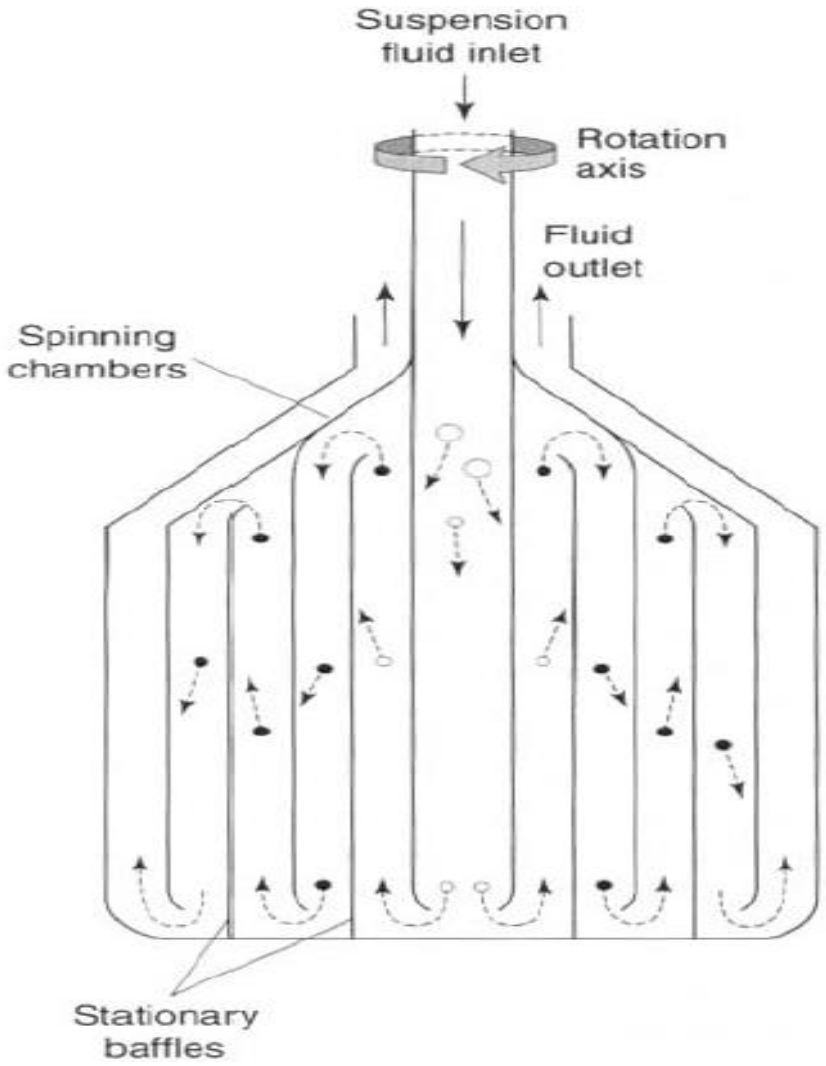


Fig. Multiple-chamber centrifuges.

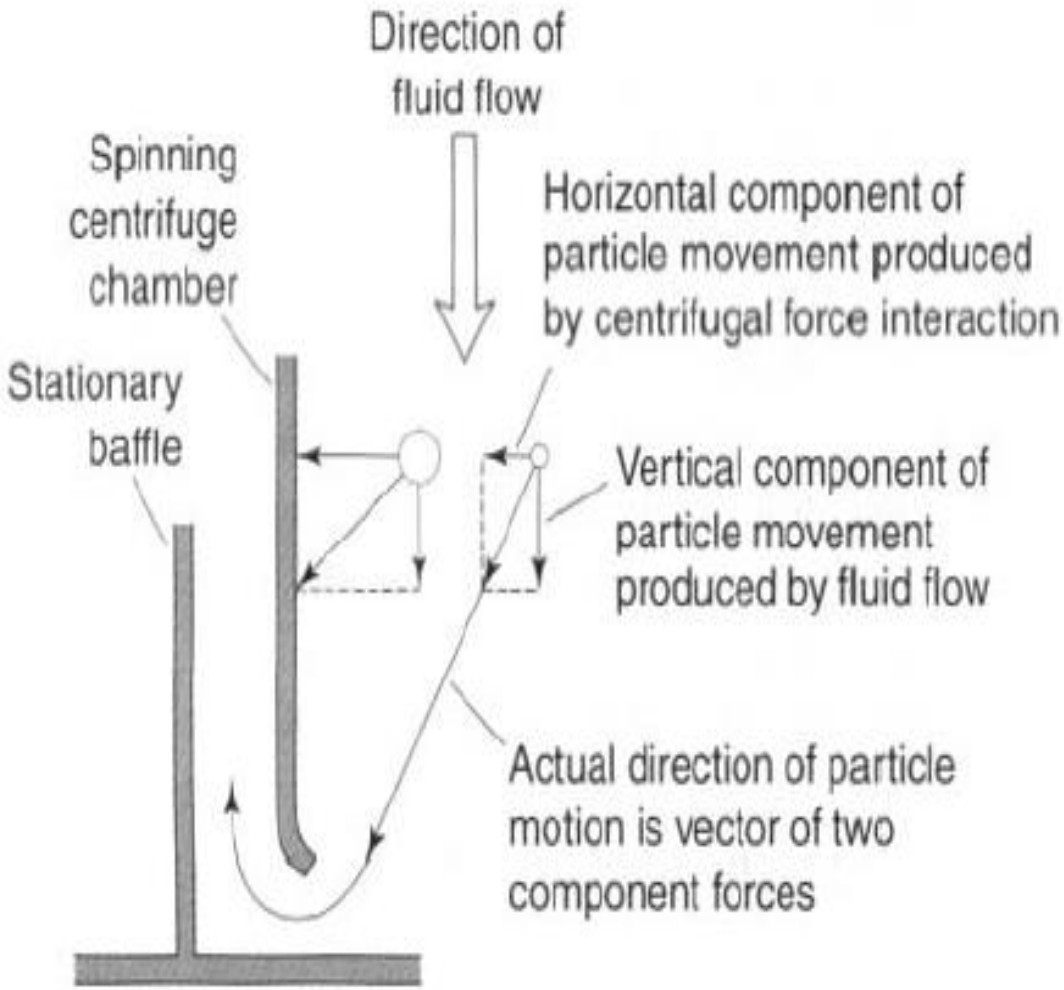
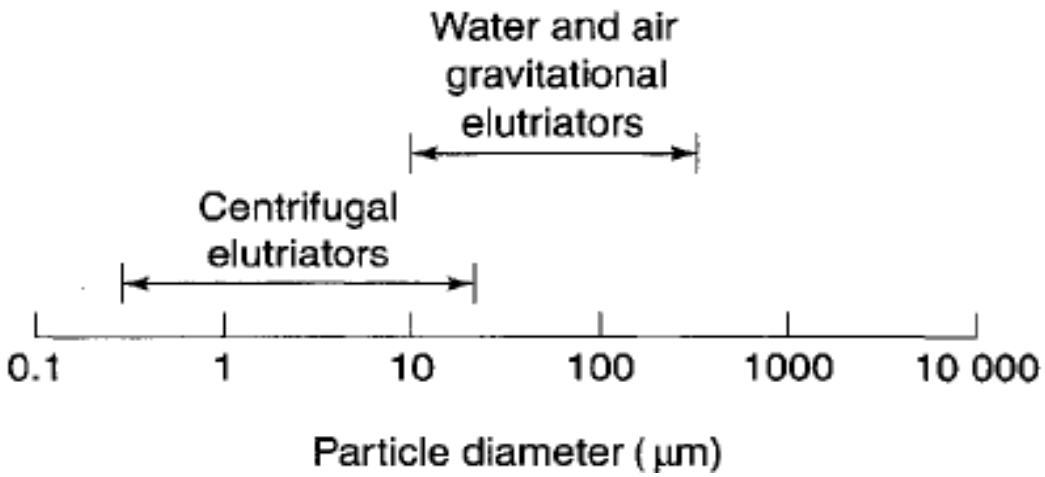


Fig. Driving forces in Multiple-chamber centrifuges.

B) Elutriation methods:

- Size range:



...

- Principles of operation
  - Fluid flows in an opposite direction to the sedimentation movement,
  - So that in gravitational elutriators particles move vertically downwards while the fluid travels vertically upwards,
  - And, particles are divided into different size fractions depending on the velocity of the fluid and size of particles,

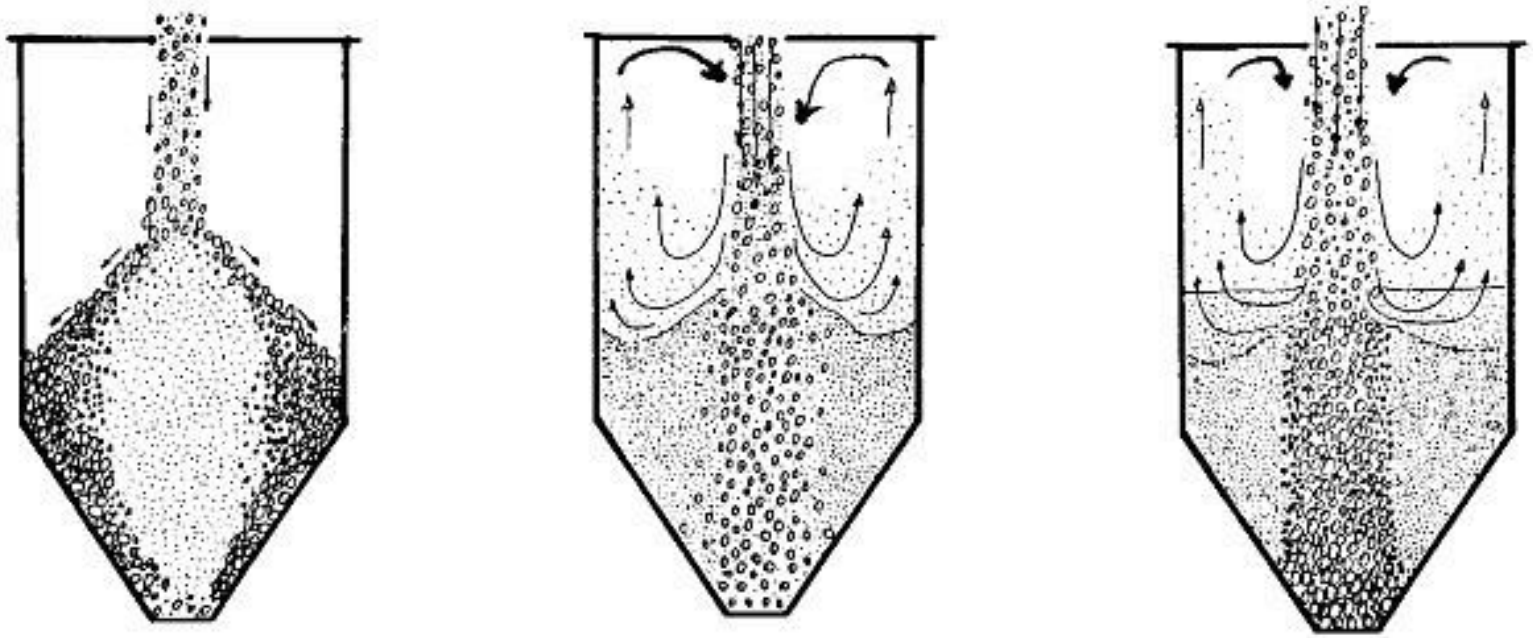


Fig. Elutriation size separation technique.

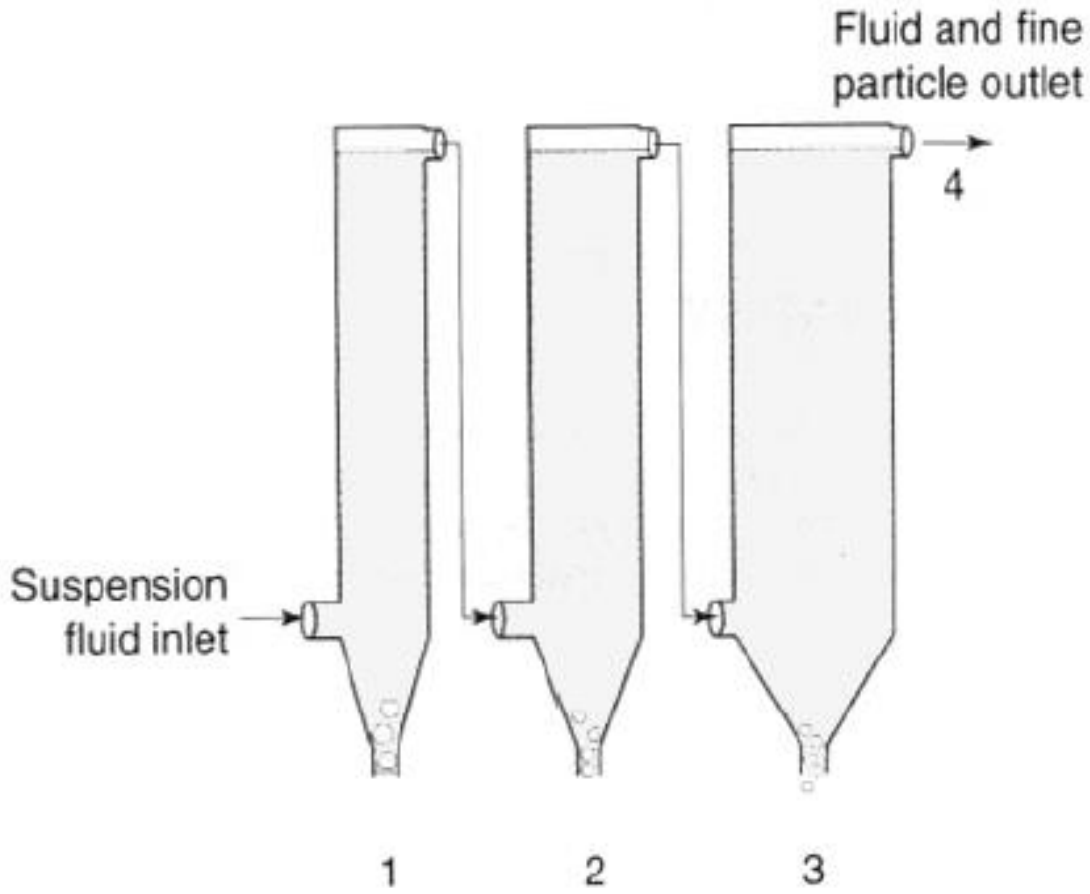
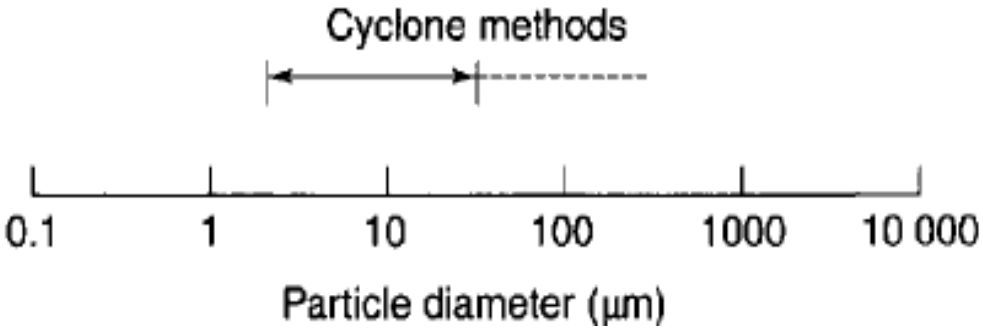


Fig. A number of elutriators connected in series to increase size separation efficiency.

C) Cyclone methods

- Size separation range:



- Principle of operation
  - The most common type is the reverse-flow cyclone,
  - Particles in air or liquid suspension are often introduced tangentially into the cylindrical **upper section** of the cyclone,
  - And, relatively high fluid velocity produces a vortex that throws solid particles out on to the walls of the cyclone.

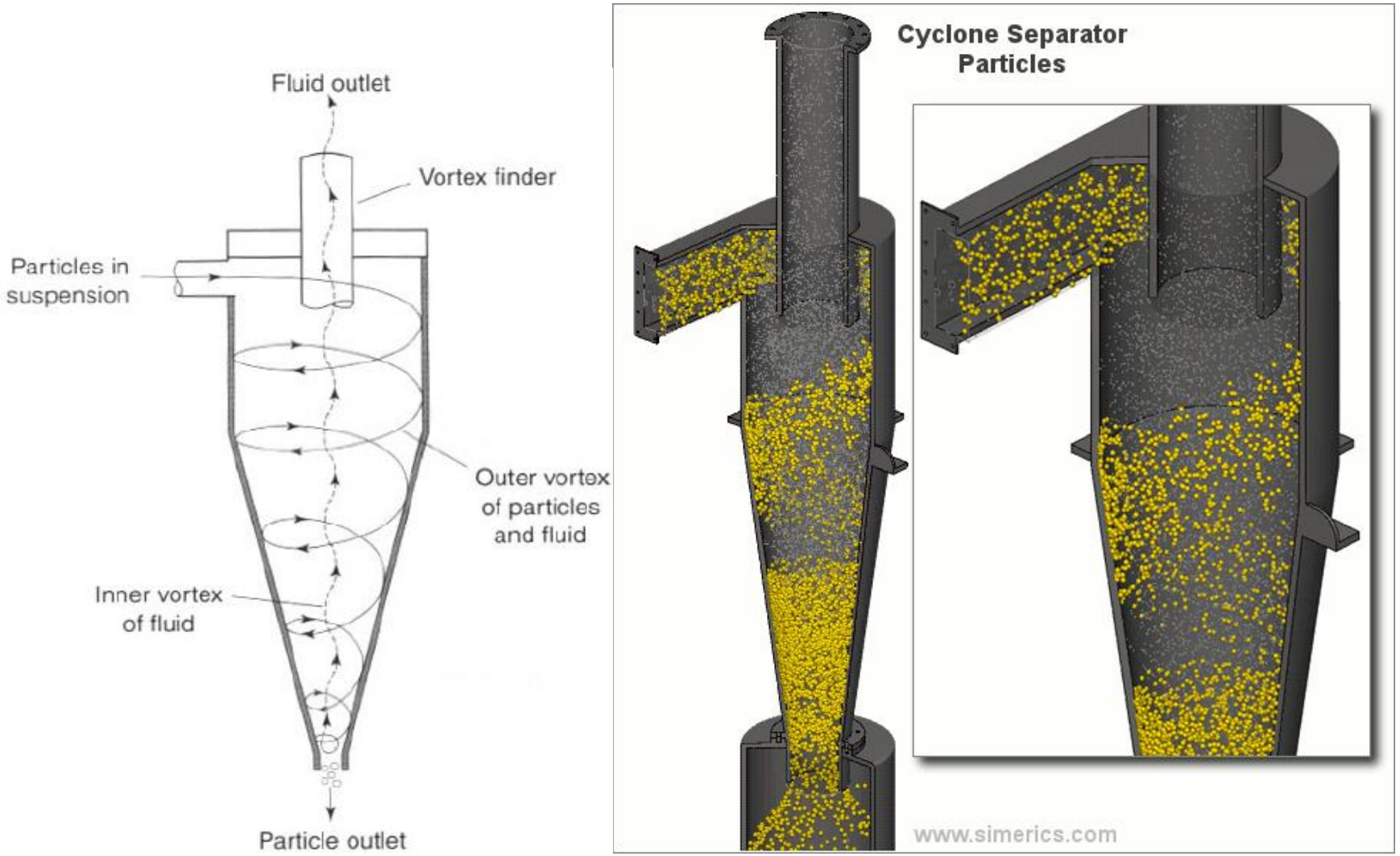


Fig. Cyclone separator (principle)

3. Mixing

- Definition:
  - The process that results in a randomization of a dissimilar particle within a system,
- Objectives:
  - Simple physical mixture
    - For the production of a blend of two or more miscible liquids or two or more uniformly divided powders

- Physical change
  - Mixing may aim at producing a change that is physical as distinct from chemical.
- Dispersion
  - E.g. the dispersion of two immiscible liquids to form an emulsion.
- Promotion of reaction
  - Encourage and control a chemical reaction.

...

Types of mixing

A) Based on the behavior of mixing:

1. Positive Mixing

   - Where substances will in time completely mix **spontaneously** and **no energy** needs to be used for this to occur
   - **Irreversible** mixing occur
   - E.g: miscible liquids, gases
   - These types of material do not create any problem in mixing

...

2. Negative Mixing

- Where **energy is required** and the components of which **will separate** unless work is done by stirring to keep them dispersed.
- Energy must be continuously input to keep maintain mixed,
- E.g. with a suspension formulation in less viscous liquids.
- More difficult to form and maintain, and require a higher degree of mixing efficiency.

...

3. Neutral Mixing

- **Work must be done** to mix them initially but usually there is **no tendency** for de-mixing to occur spontaneously
- They are static in their behavior
- E.g. mixed powders, pastes and ointments

NB: The type of mixture might change during processing!!

...

B) Based on the states of existence:

1. Liquid mixing
2. Powder mixing
3. Semisolid mixing

1. Liquid Mixing

- Mixing of liquids and liquids
  - Mixing of two miscible liquids → Solution
  - Mixing of two immiscible liquids → Emulsion
- Mixing of liquids and solids
  - Mixing of liquids and soluble solids → Solution
  - Mixing of liquids and insoluble solids → Suspension

2. Powder Mixing

- Neutral type of mixing
- The degree of mixing will increase with the length of time for which mixing is done,
  - Optimal time required ??
- Powder mixing is employed in formulation of powders, capsules and tablets

3. Semisolid Mixing

- Many semisolids form neutral mixture because they have no tendency to segregate but sedimentation occur in certain circumstances

Process of mixing

- To consider the principles of the mixing process, a situation will be considered:
  - Where there are equal quantities of two powdered components of the same size, shape and density
  - The only difference between them being their color

...

- Ideal situation or 'perfect mix’ be produced -
  - when each particle lies as closely as possible in contact with a particle of the other component.

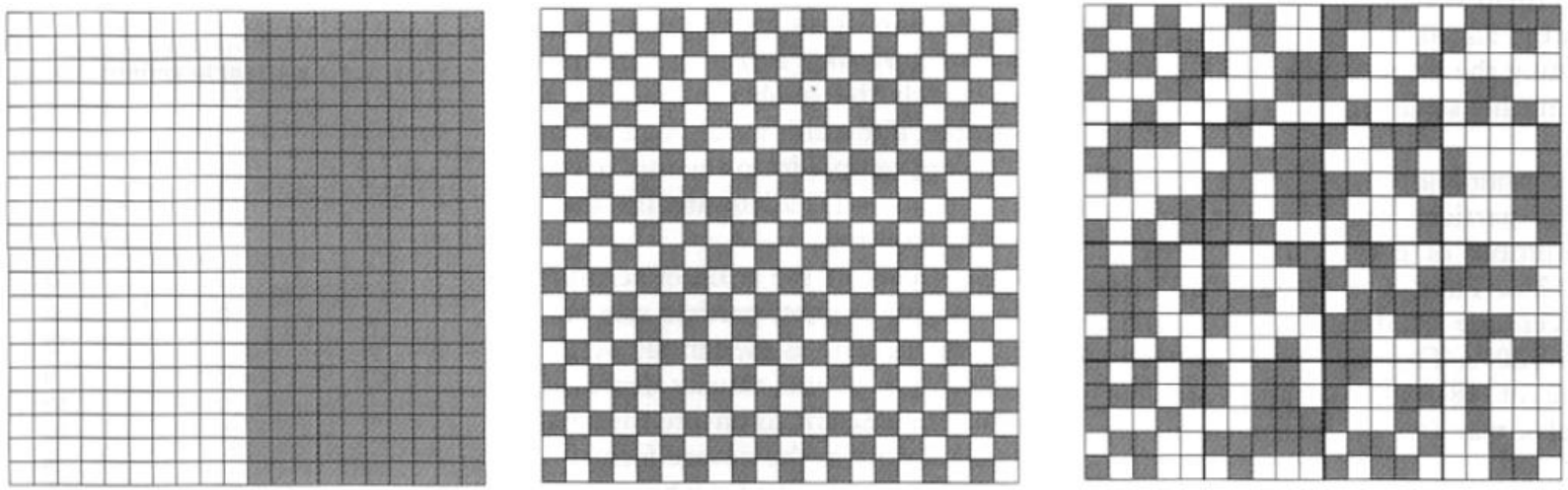


Fig. Different states of powder mixing, Complete segregation (left), An ideal or 'perfect' mix (middle) A random mix (right).

Scale of scrutiny

- Defining the degree of mixing means nothing if the sampling size from which the components will be analyzed has not been defined.
  - The larger the sample size, the higher will be the chances of concluding that the powder mixture is homogeneous.
  - And, vice versa.
  - The sampling size, or scale of scrutiny, must always be defined according to the use that will be made of the mixture.

- Definition:
  - For pharmaceuticals products, the sampling size (scale of scrutiny) will have to be in line with the dose to be contained in the dosage form or the weight of dosage unit.
  - The amount of material within which the quality of mixing is important.
  - For example, if the unit weight of a tablet is 200 mg then a 200 mg sample from the mix needs to be analyzed to see if mixing is adequate; the scale of scrutiny is, therefore, 200 mg.

...

- The number of particles in the scale of scrutiny will depend on the sample weight, particle size and particle density
  - Will increase as the sample weight increases and the particle size and density decrease.
  - The more particles present in a unit dose/scale of scrutiny the lower the deviation in content.

...

- The factors that influence mixing can also be treated statistically,
  - Considering samples taken from a random mix in which the particles are all of the same size, shape and density,
  - The variation in the proportion of a component in samples taken from the random mix can be calculated from:

$$SD = \sqrt{\frac{p(1-p)}{n}}$$

- SD is the standard deviation
- p is the proportion of the component in the total mix and
- n is the total number of particles

...

- From the above eq.,
  - As the number of particles present in the sample increases the content standard deviation decreases.
  - As p is decreased the value of the content standard deviation decreases,
    - Which may lead to the incorrect conclusion that it is beneficial to have a low proportion of the active component.

...

- A more useful parameter to determine is the percentage coefficient of variation (%CV),
- %CV indicates the average deviation as a percentage of the mean amount of active component in the samples.
  - %CV = (content standard deviation/mean content) x 100.
  - The value of %CV will increase as p decreases.

- For n = 100 000 and p = 0.5,
  - SD =
  - %CV =
- For n = 100 000 and p = 0.001,
  - SD =
  - %CV =

...

Evaluation of the degree of mixing

- Manufacturers require some means of monitoring a mixing process for a variety of reasons:
  - To indicate the degree/extent of mixing,
  - To follow a mixing process,
  - To indicate when sufficient mixing has occurred,
  - To assess the efficiency of a mixer,
  - To determine the mixing time required for a particular process,

...

- Degree of mixing commonly evaluated by 'mixing index'
  - Which compares the content SD of samples taken from a mix under investigation (S_{ACT}) with that of samples from a fully random mix (S_R)
  - The simplest form of a **mixing index (M)** can be calculated as:

$$M = \frac{S_R}{S_{ACT}}$$

$$SD = \sqrt{\frac{p(1-p)}{n}}$$

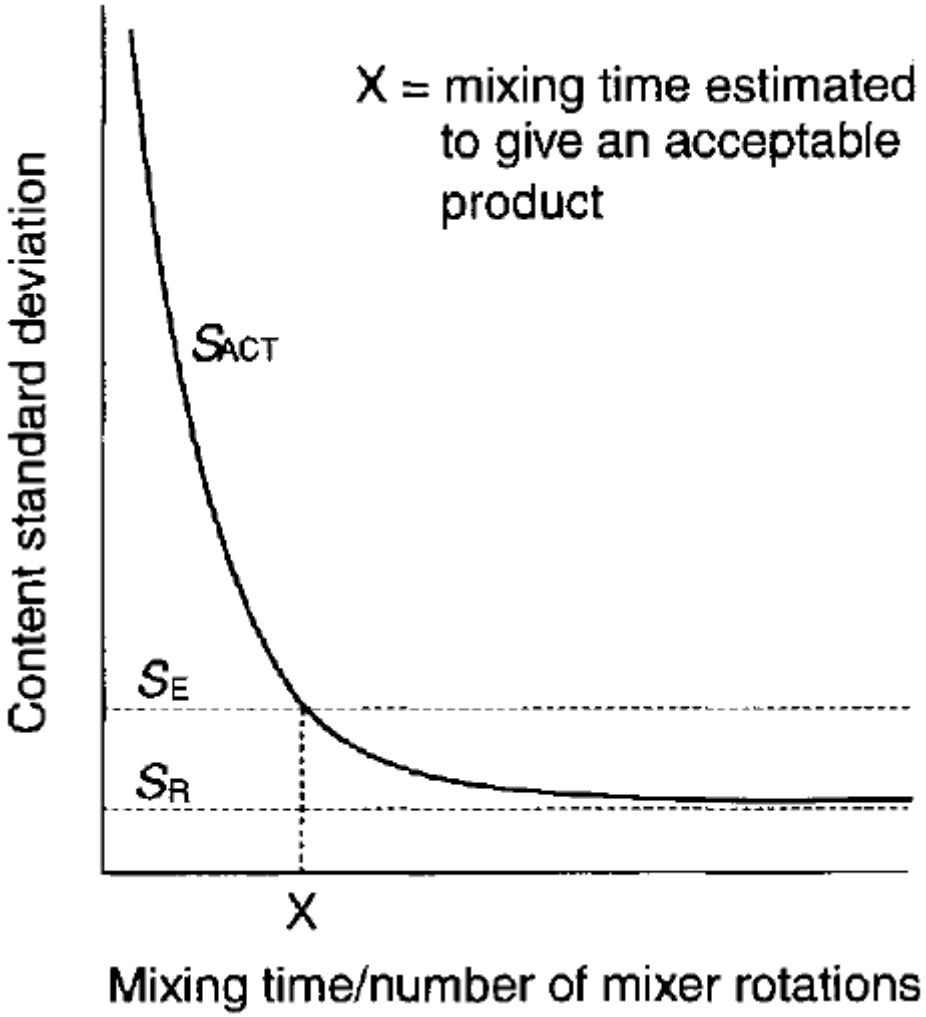
...

- In order to evaluate a mixing process in the above way there are two basic requirements:
  - Sufficient number of samples must be removed and analyzed
  - Suitable analytical technique

...

- When mixing formulations where p is high it is possible to achieve an acceptably low variation in content without obtaining a random mix

- Thus it may be possible to stop the mixing process before a random mix is achieved and thereby reduce manufacturing costs


X = mixing time estimated to give an acceptable product
Content standard deviation
S_{ACT}
S_E
S_R
X
Mixing time/number of mixer rotations

Factors affecting mixing

1) Particle size

- Percolation segregation: Smaller particles tend to fall through the voids between larger ones,
- Trajectory segregation: larger particles will tend to have greater kinetic energy and move greater distances than smaller particles,
- Elutriation segregation/dusting out: very small particles ('dust') in a mix may tend to be 'blown' upwards by turbulent air currents.

2) Density

- If components are of different density, the more dense material will have a tendency to move downwards even if the particle sizes are similar.

- The effect of density on percolation segregation may be potentiated if the more dense particles are also smaller

3) Shape

- Spherical particles exhibit the greatest flowability and are therefore more easily mixed, but they also segregate more easily than non-spherical particles
- Irregularly particles may become interlocked, reducing the tendency to segregate once mixing has occurred
- Non-spherical particles will also have a greater surface area to weight ratio, which will tend to decrease segregation by increasing any cohesive effects

4) Time of mixing

- Non-segregating mixes will improve with continued increases in mixing time
- This may not, however, occur for segregating mixes, where there is often an optimum mixing time
  - This is because the factors causing segregation generally require longer to take effect than the time needed to produce a reasonable degree of mixing.

...

- Minimizing segregation:
  - Selection of particular size fractions to achieve drug and excipients of the same narrow particle size range
  - Milling of components (size reduction)
    - to reduce the particle size range (this may need to be followed by a sieving stage to remove fines) or
    - to ensure that all particles are below approximately 30 μm

- Controlled crystallization during production of the drug/excipients to give components of a particular crystal shape or size range
- Selection of excipients which have a density similar to the active component (s)
- Reduce the extent to which the powder mass is subjected to vibration or movement after mixing
- Use filling machine hoppers designed so that powder residence time is minimized

...

- Use equipment where several operations can be carried out without transferring the mix,
  - e.g. a fluidized-bed drier or a high-speed mixer/granulator for mixing and granulating
- Production of an 'ordered' mix

Mixing mechanisms

1. Powder Mixing

- There are three main mechanisms by which powder mixing occurs:
  - Convection
  - Shear
  - Diffusion

...

A. Convective mixing

- Arises when there is the transfer of relatively large groups of particles from one part of the powder bed to another
  - contributes mainly to the macroscopic mixing of powder mixtures and
  - tends to produce a large degree of mixing fairly quickly

E.g. Occur when a mixer blade or paddle moves through the mix

B. Shear mixing

- Occurs when a layer of material moves/flows over another layer
  - Due to the removal of a mass by convective mixing creating an unstable shear/slip plane, which causes the powder bed to collapse.
- It may also occur in high shear mixers or tumbling mixers, where the action of the mixer induces velocity gradients within the powder bed and hence 'shearing' of one layer over another

...

C. Diffusive mixing

- When a powder bed is forced to move or flow it will 'dilate', i.e. the volume occupied by the bed will increase,
- Under these circumstances there is the potential for the particles to fall under gravity through the voids created.
- Diffusive mixing having the potential to produce a random mix.
- Generally results in a low rate of mixing.

...

- All three mixing mechanisms are likely to occur in a mixing operation
- Which one predominates and the extent to which each occurs will depend on:
  - The mixer type
  - Mixing process conditions (mixer load, speed etc.)
  - The flowability of the powder components

...

2. *Liquid mixing*

- The three main mechanisms by which liquids are mixed are:
  - Bulk transport
  - Turbulent mixing
  - Molecular diffusion

...

A. Bulk transport

- Movement of a relatively large portion of the material being mixed from one location in the system to another constitutes.

- Tends to produce a large degree of mixing fairly quickly, but leaves the liquid within the moving material unmixed.

...

B. Turbulent mixing

- Arises from the haphazard movement of molecules when forced to move in a turbulent manner,
- The constant changes in speed and direction of movement means that induced turbulence is a highly effective mechanism for mixing.
- Within a turbulent fluid there are, however, small groups of molecules moving together as a unit, referred to as **eddies**

...

- Turbulent mixing alone may leave:
  - Small unmixed areas within the eddies, and
  - In areas near the container surface which will exhibit streamlined flow.

...

C. Molecular diffusion

- The primary mechanism for mixing at molecular level.
- Will occur with miscible fluids wherever a concentration gradient exists and will eventually produce a well-mixed product.
- Considerable **time** may be required if this is the only mixing mechanism.

- In most mixers all the above three mechanisms will occur.

- Mixing Equipments
  - In small scale
    - Ointment tile and spatula
    - Mortar and pestle
  - In industrial scales
    - Impeller/propeller mixer
    - Tumbling mixer (V-shape, Y cone, etc)
    - Fluidized bed mixer

...

1. Liquid mixers

- Shaker mixer:
  - The material present is agitated either by an oscillatory or by a rotary movement.
  - Oscillatory is applicable for small scale work whereas rotary is for large scale work.

- Propeller mixers:
  - Are the most widely used form of mixers for liquids of low viscosity.
  - The size of the propeller is very small as compared to the size of the container and rotate at high speed (~8000 rpm).
  - The high speed of the propeller may lead to undesirable vortex formation and entrapment of air.

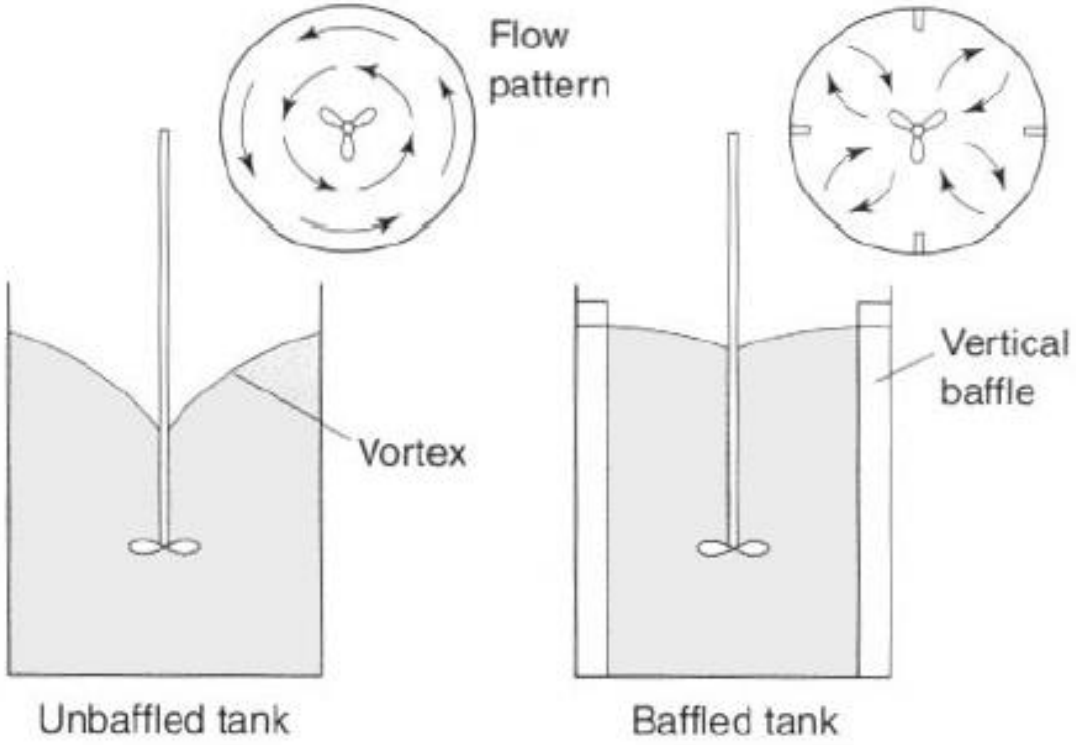


Fig. Propeller mixer with (a) unbaffled tank and (b) baffled tank.

- Turbine mixers:
  - Consists of a circular disc impeller to which a number of short, straight or curved blades are attached.
  - Used for mixing of liquids of high viscosity.

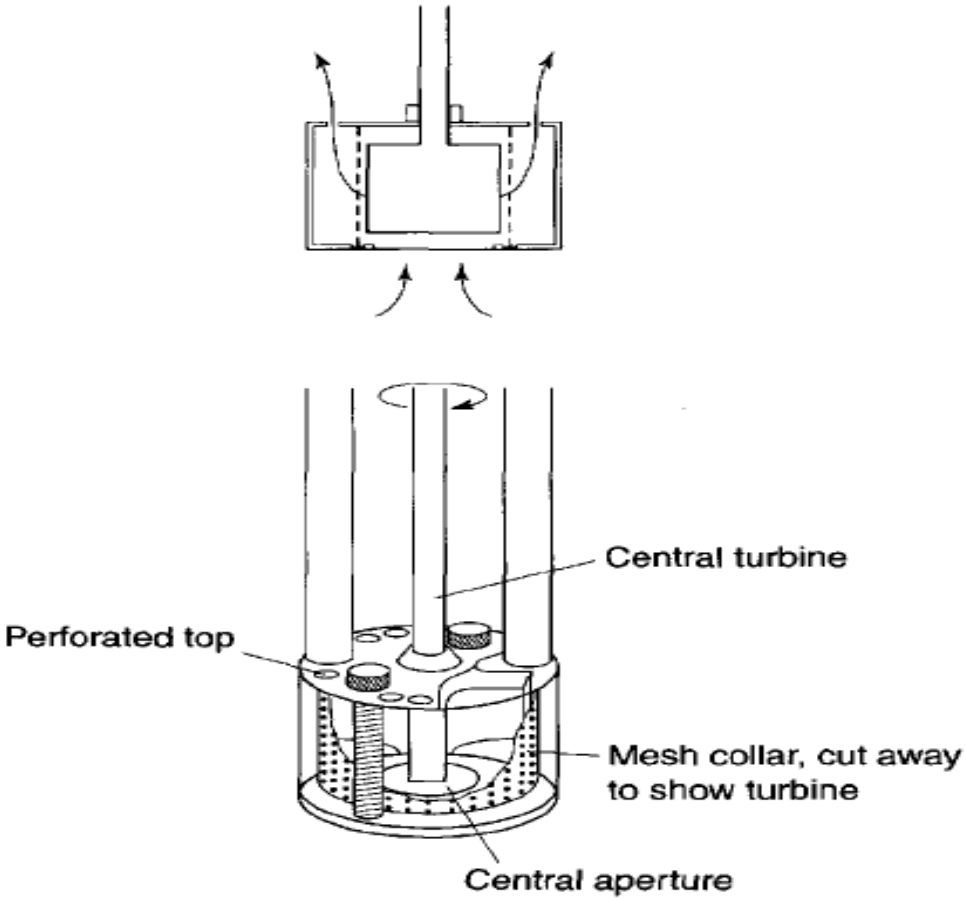


Fig. Turbine mixer

- Paddle mixers:
  - A number of paddles are used which consist of flat blades attached to a vertical shaft and rotate at a slow speed of 100 rpm or less.
  - The blades have a large surface area in relation to the container in which they are employed
    - This helps them rotate close to the walls of the container and effectively mix the viscous liquids or semisolids.

2. Powder mixers

- Tumbling mixers/blenders
  - There are many different designs of tumbling mixer, e.g. double-cone mixers, twin-shell mixers, cube mixers, Y-cone mixers and drum mixers.
  - Mixing containers are generally mounted so that they can be rotated about an axis.
  - Mixing mechanism is mainly by shear mixing and diffusive mixing.

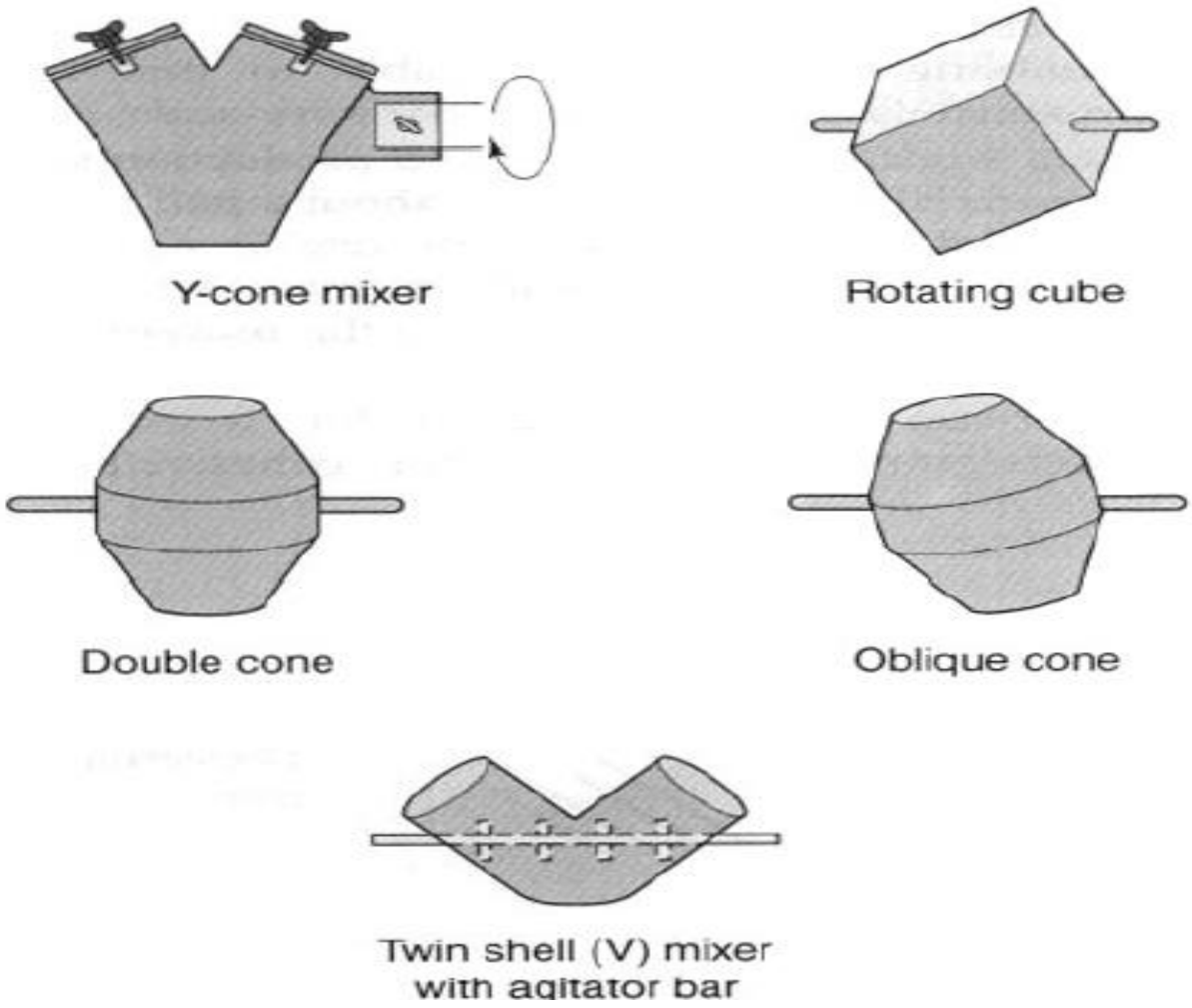


Fig. Different designs of the tumbling mixers.

- The efficiency of tumbling mixer is highly dependent on the speed of rotation
  - Too slow => doesn't produce desired intense tumbling nor does it generate rapid shear rates
  - Too rapid => produce centrifugal force sufficient to hold powder to the side of mixer and reduce efficiency
- The optimum rate of rotation depends on the size and shape of the tumbler and also on the type of material being mixed.

- Agitator mixers
  - This type of mixer depends on the motion of a blade or paddle through the product, and hence the main mixing mechanism is convection.
  - Examples include the Ribbon mixer and the Nauta mixer.

- Ribbon mixer:
  - Mixing is achieved by the rotation of helical blades in a hemispherical trough.
- Nauta mixer:
  - Consists of a conical vessel fitted at the base with a rotating screw, which is fastened to the end of a rotating arm at the upper end.
  - The screw conveys the material to near the top, where it cascades back into the mass.
  - Combines convective mixing and shear and diffusive mixing.

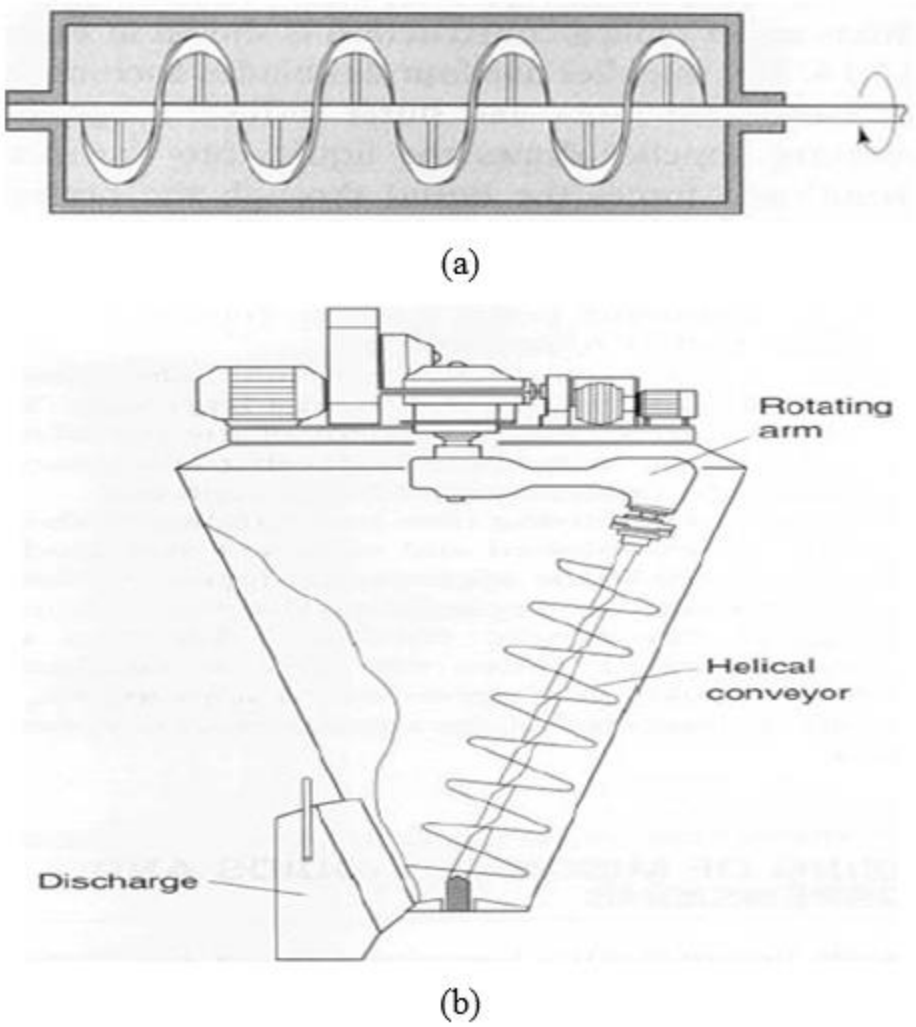


Fig. Ribbon mixer (a) and Nautamixer (b).

- High-speed mixer-granulators
  - It can both mix and granulate a product,
    - Thereby, removing the need to transfer the product between pieces of equipment and so reducing the opportunity for segregation to occur.
  - The centrally mounted impeller blade at the bottom of the mixer rotates at high speed, throwing the material towards the mixer bowl wall by centrifugal force.
  - The material is then forced upwards before dropping back down towards the center of the mixer.

- The particulate movement within the bowl tends to mix the components quickly owing to high **shear** forces (arising from the high velocity) and the expansion in bed volume that allows **diffusive** mixing.

- Once mixed, granulating agent can be added and granules formed *in situ* using a slower impeller speed and the action of the side-mounted chopper blade.

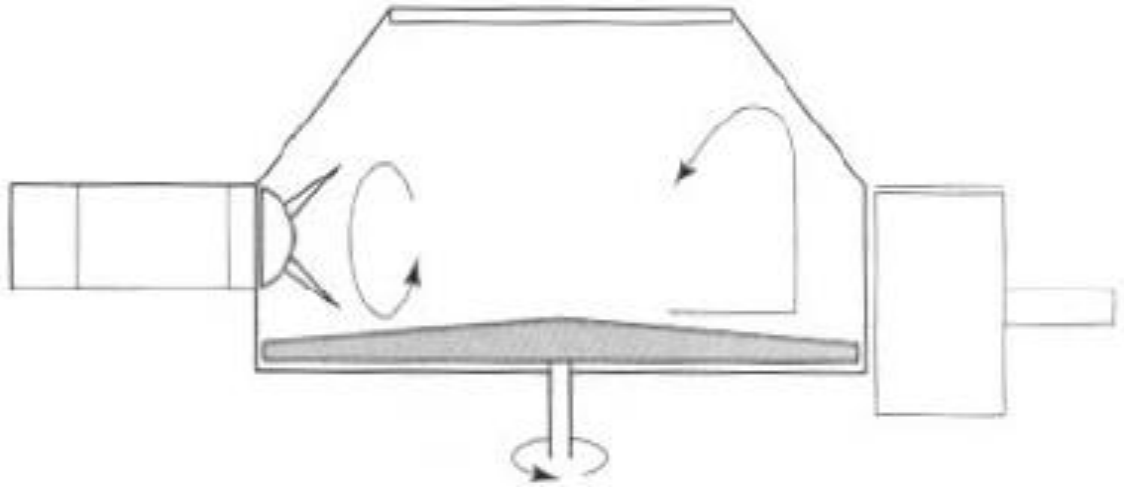


Fig. Diagrammatic representation of a high-speed mixer-granulator.

3. Mixers for semisolids

- Sigma-blade mixer
  - This robust mixer will deal with stiff pastes and ointments
  - Depends for its action on the close intermeshing of the two blades which resemble the Greek letter sigma in shape.

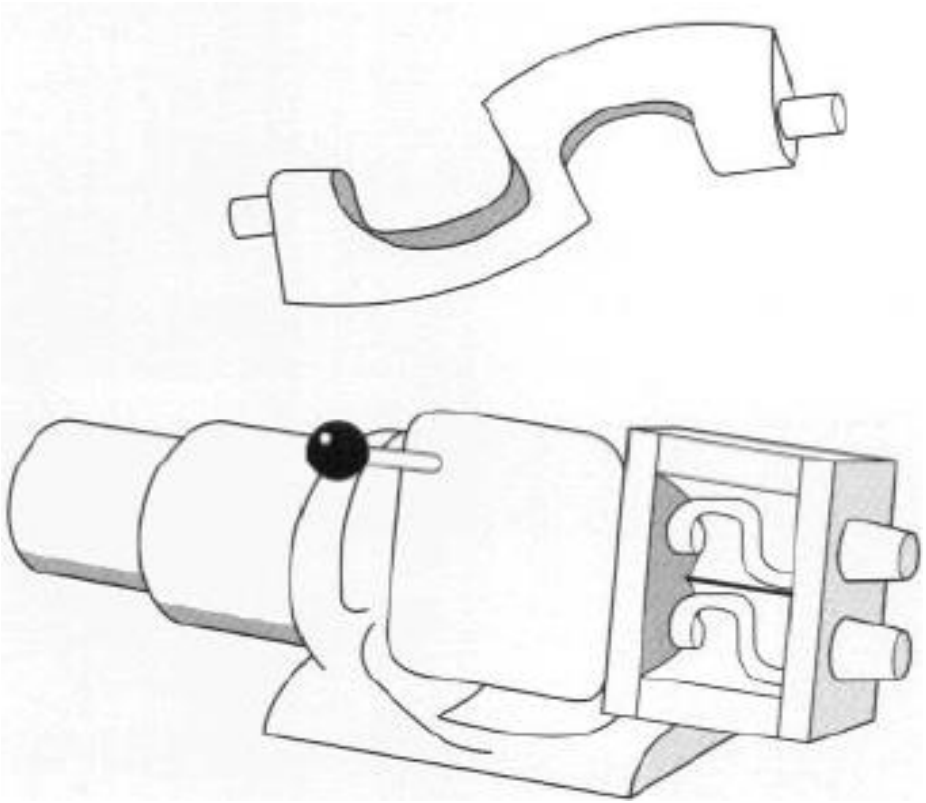


Fig. Sigma blade mixer.

- Factors considered to select type of mixer
  - The physical property of material to be mixed

    Eg: density, Viscosity, Miscibility
  - Economic consideration
    - Time required for mixing
    - Power consumption
    - The cost of the equipment and its maintenance

4. Drying

- Definition
  - Drying is the removal of a liquid from a material by the application of heat,
  - It is accomplished by the transfer of a liquid from a surface into an unsaturated vapor phase,
  - Drying involves both heat and mass transfer.

...

- Drying and evaporation are distinguishable merely by the relative quantities of liquid removed from the solid.
- To be considered drying, the final product must be a solid.
- To achieve this there must be a source of heat and a sink of vapor thus produced.

...

- Purpose of drying

1. In the preparation of granules
2. To prepare certain product such as powdered extracts, dried anhydrous lactose and dried vegetable drugs
3. To reduce bulk and weight, lowering the cost of transportation and storage
4. To preserve products
5. To minimize chemical reaction
6. To facilitate size reduction

Factors affecting drying

- The vapor carrying capacity of the air or gas stream passing over the drying material,
  - This carrying capacity determines:
    - The rate of drying
    - The extent of drying

- Driving force
  - Humidity differential => diffusion of moisture
  - Temperature differential => for heat transfer
- Air flow and inlet air temperature
- Rate of convection and radiation heat transfer
- Thickness of the material being dried

- Air velocity
  - Increased air velocity speed up rate of drying by increasing coefficient of mass transfer
- Dehumidification of inlet air
- Molecular and capillary structure of the solid

...

A. Drying of wet solids

a) Moisture content of wet solids

- The MC of a wet solid is expressed as kilograms of moisture associated with 1 kg of the moisture-free or 'bone-dry' solid,

- It is sometimes calculated as a percentage moisture content (%MC):

$$\%\boldsymbol{MC} = \frac{\textbf{Weight of water in sample}}{\textbf{Weight of dry sample}} \times \mathbf{100}$$

...

b) Total moisture content

- The total amount of liquid associated with a wet solid
  - The easily removable water is known as the free moisture content (unbound water) and
  - the moisture which is more difficult to remove in practice is the equilibrium moisture content (Bound water)

...

c) Equilibrium moisture content

- The moisture content present in a solid under steady-state ambient conditions
- Its value changes with temperature, humidity and the nature of the solid

...

d) Relative humidity (RH) of air

- The percentage RH may be defined as:

$$\%RH = \frac{\textbf{Vapor pressure of water in air}}{\textbf{Vapor pressure of water in air saturated at same } T^o} \times 100$$

- This is approximately equal to the percentage saturation, which is the ratio:

$$\frac{\textbf{Mass of vapor present per kg of dry air}}{\textbf{Mass of vapor required to saturate 1 kg of air at same } T^o} \times 100$$

...

e) Moisture content of air

- The moisture content expressed as amount of water per kg of 'bone-dry‘ air
- Unlike RH, moisture content is not altered by change of temperature alone, only if further moisture is taken up by the air

...

f) Loss on drying (LOD)

- This is an expression of moisture content on a wet weight basis which is calculated as follows.

$$\%\boldsymbol{LOD} = \frac{\textbf{Weight of water in sample}}{\textbf{Total weight of wet sample}} \times \mathbf{100}$$

- Loss of water from wet solids
  - Unbound water is easily lost by evaporation until the equilibrium moisture content of the solid is reached
  - The only way to reduce the moisture content of the solid is to reduce the relative humidity of the ambient air
    - On a large scale with an air-conditioning system
    - On a small scale with desiccators

- Moisture may be regained very quickly from the atmosphere if a 'dry' solid is exposed to ambient air
  - It is unnecessary to 'over dry' a product
- If a low residual moisture content is necessary because of hydrolytic instability in the material
  - The dried product must be efficiently sealed

Drying Methods for wet solids

- When considering how to dry a material, the following points should be considered:
  - Heat sensitivity of the material being dried
  - Physical characteristics of the material
  - The necessity for asepsis
  - Nature of the liquid to be removed
  - The scale of the operation
  - Available sources of heat (steam, electrical).

...

- The general principles for efficient drying:
  - Large surface area for heat transfer
  - Efficient heat transfer per unit area
  - Efficient mass transfer of evaporated water through any surrounding boundary layers
  - Efficient vapor removal, i.e. low relative humidity air at adequate velocity

...

- Three basic methods of drying for wet solids:

1. Convective drying
2. Conductive drying
3. Radiation drying

...

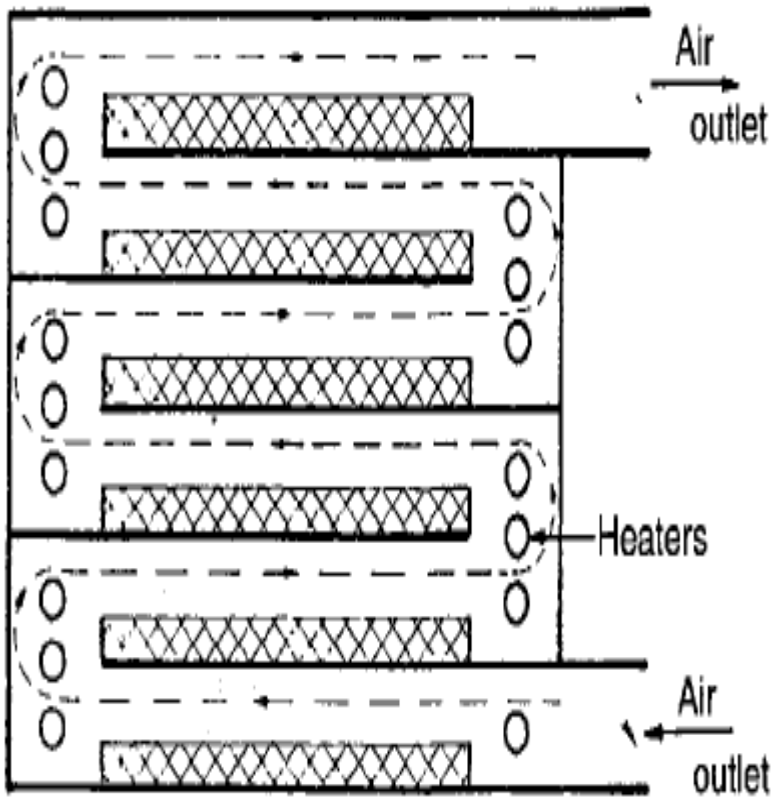
Convective drying

1) Fixed (or static) bed convective drying

- There is no relative movement among the solid particles being dried but there may be bulk motion of the entire drying mass
  - Only a fraction of the total number of particles is directly exposed to heat source
- The exposed surface can be increased by decreasing the thickness of the bed

a) Tray Dryers

- Shelf, cabinet, or compartment dryers
- Consists of cabinet in which the material to be dried is spread on tiers of trays



...

- Tray dryer classified into:
  - Direct tray dryer: in which heating is accomplished by the forced circulation of large volume of heated air.
  - Indirect tray dryer: utilizes heated shelves or radiant heat sources inside drying chamber to evaporate the moisture which is then removed by either vacuum pump or small amount of circulating gas.

b) Truck dryer

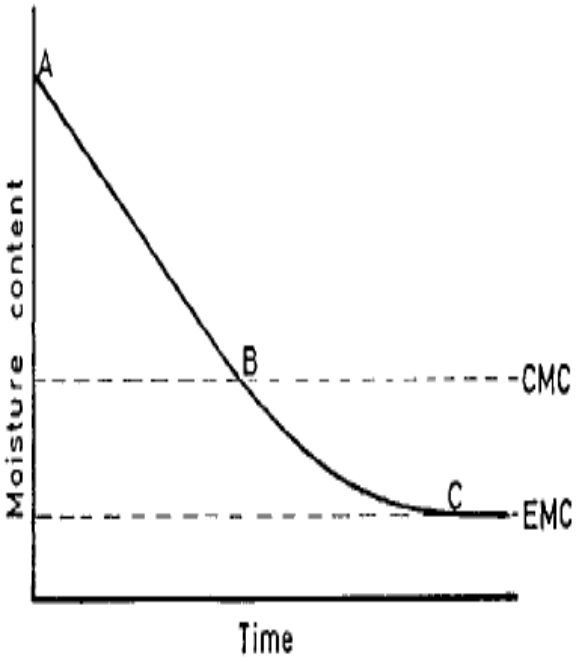
- A truck dryer is one in which the trays are loaded on truck (racks equipped with wheels) which can be rolled into and out of the drying cabinet,
- Truck dryer preferred over tray dryer because it offers greater convenience in loading and unloading,
- Both tray and truck dryers are batch procedures.

c) Tunnel and Convey dryers

- Tunnel and conveyor dryers are another static bed dryer which are semi continuous and continuous respectively.
- Conveyor dryer is more suitable to handle large volume of materials.

...

- Rate of drying in fixed beds
  - Change in moisture content is as function of time



- Constant-rate period (A to B)
  - Most substances dry at a similar rate in the constant-rate period
  - The evaporation rate from the drying bed is similar to that of the solvent alone from a free liquid surface under the same conditions
    - The evaporation takes place from the wet surface of the solid and that the surface remains wet in this period
  - Controlling factors are the rate at which heat can be transferred and the rate of removal of the vapor

...

- First falling-rate period (B to C)
  - As moisture is removed from the surface, a point will be reached when the rate of vaporization is insufficient to saturate the air in contact with the surface.
  - Consequently, the rate of drying decreases continuously.

- Second falling-rate period

  - Any moisture that remains within the drying bed at the end of the first falling-rate period is unable to move, so that drying cannot take place on the surface

  - Hence, the plane of vaporization retreats from the surface into the body of the solid, and the drying rate depends on the movement of the vapor through the pores of the bed to the surface, in general by molecular diffusion

...

2) Dynamic convective driers

- Fluidized bed dryers
  - It comprises of a top fluidizing chamber and a bottom air distribution chamber separated by a special designed perforated plate
  - System in which the solid particles are partially suspended in an upward moving gas stream
  - The feed of wet materials is dried by intimate contact with hot air when the material is in a fluidized state

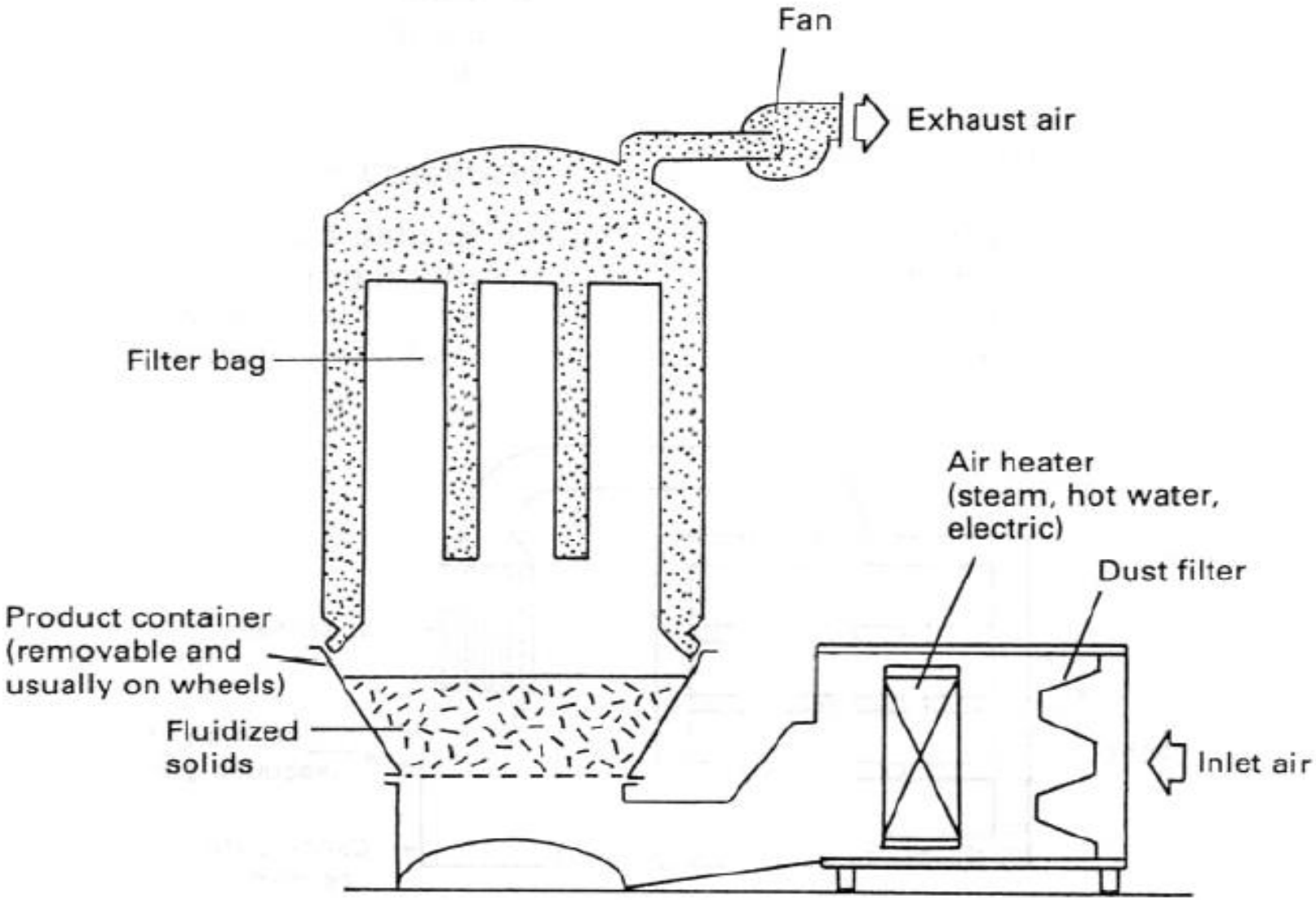


Fig. Fluidized bed dryer.

Fig. Fluidized bed dryer.

- Classified into:
  - Vertical fluidized bed dryer
  - Horizontal vibrating conveyor dryer

- Advantages of fluidized-bed drying
  - Efficient heat and mass transfer give high drying rates.
  - The fluidized state of the bed ensures that drying occurs from the surface of all the individual particles and not just from the surface of the bed.
    - Hence, most of the drying will be at constant rate and the falling-rate period is very short
  - The temperature of a fluidized bed is uniform throughout and can be controlled precisely.

- The turbulence in a fluidized bed causes some attrition to the surface of the granule.
  - This produces a more spherical free-flowing product
- The containers can be mobile, making handling and movement around the production area simple and so reducing labor costs
- Short drying times mean that the unit has a high output

- Disadvantages of fluidized-bed drying
  - The turbulence of the fluidized state may cause excessive attrition of some materials, with damage to some granules and the production of too much dust
  - Fine particles may become entrained in the fluidizing air and must be collected by bag filters
  - The vigorous movement of particles in hot dry air can lead to the generation of static electricity charges

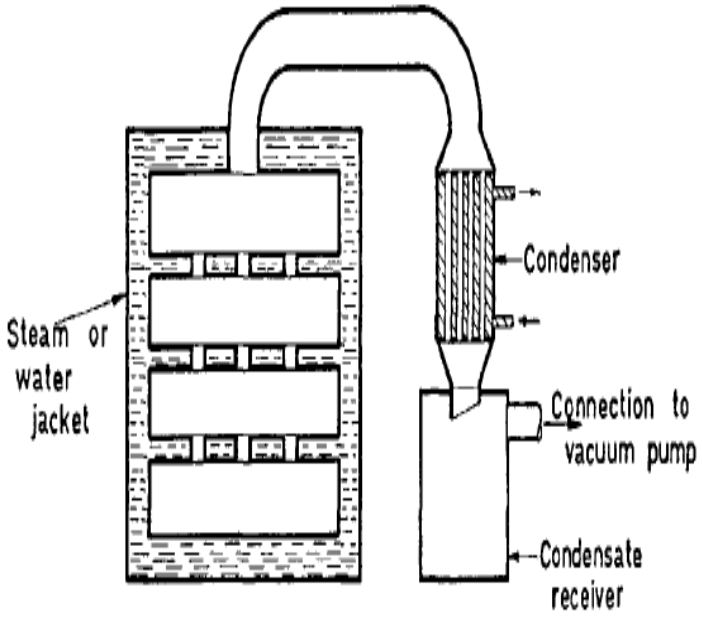
...

Conductive drying

- Vacuum oven
  - The vacuum oven consists of a jacketed vessel sufficiently stout in construction to withstand vacuum within the oven and steam pressure in the jacket
  - The supports for the shelves form part of the jacket, giving a larger area for conduction heat transfer.

- The oven is connected through a condenser and liquid receiver to a vacuum pump

- If the liquid to be removed is water and the pump is of the ejector type that can handle water vapor, the pump can be connected directly to the oven.



...

- The main advantage of a vacuum oven is that drying takes place at a low temperature, and as there is little air present there is minimum risk of oxidation

- The temperature of the drying solid will rise to the steam or water temperature at the end of the drying

- Vacuum tumbling drier
  - One design of tumbler drier resembles a large Y-cone mixer
  - The vessel is steam jacketed and is connected to a vacuum
  - Heat transfer rates in this equipment are much higher than in a conventional vacuum oven

...

Radiation drying

- Radiant heat transmission
  - Heat transmission by radiation differs from heat transfer by conduction or convection in that no transfer medium need be present
  - Heat energy in the form of radiation can cross empty space or travel through the atmosphere virtually without loss
  - If it falls on a body capable of absorbing it then it appears as heat

...

- Infrared radiation
  - Infrared heating has been used in the past to dry pharmaceutical products such as wet granules
  - It suffers from the disadvantage that it is absorbed very quickly and does not penetrate far into the wet mass
  - The surface layers dry quickly and the absorption of further energy then raises the temperature of the dry material to a high value, which is often detrimental to the product.

...

- Microwave radiation
  - Microwave radiation in the wavelength range 10 nm to 1 nm penetrates much better than IR radiation
  - Microwave driers are finding some application in the pharmaceutical industry

- Generation and action of microwaves
  - Microwaves are produced by an electronic device known as a magnetron
  - Microwave energy can be reflected down a rectangular duct (termed a waveguide)
  - The penetration of microwaves into the wet product is so good that heat is generated uniformly within the solid

- When microwaves fall on substances of suitable electronic structure (small polar molecules, such as water)
  - The electrons in the molecule attempt to resonate in sympathy with the radiation and the resulting molecular 'friction' results in the generation of heat
- Dry solids do not resonate, so further heating may be avoided once the water is removed

...

- Advantages of microwave drying:
  - It provides rapid drying at fairly low temperatures
  - The thermal efficiency is high, as the drier casing and the air remain cool
  - The bed is stationary, avoiding the problems of dust and attrition.
  - Solute migration is reduced as there is uniform heating of the wet mass.
  - Equipment is highly efficient and refined
  - Granulation end-point is possible by measuring the residual microwave energy

...

- Disadvantages of microwave drying:
  - The batch size of commercial production microwave driers is smaller than those available for fluidized-bed driers.
  - Care must be taken to shield operators from the microwave radiation

Driers for dilute solutions and suspensions

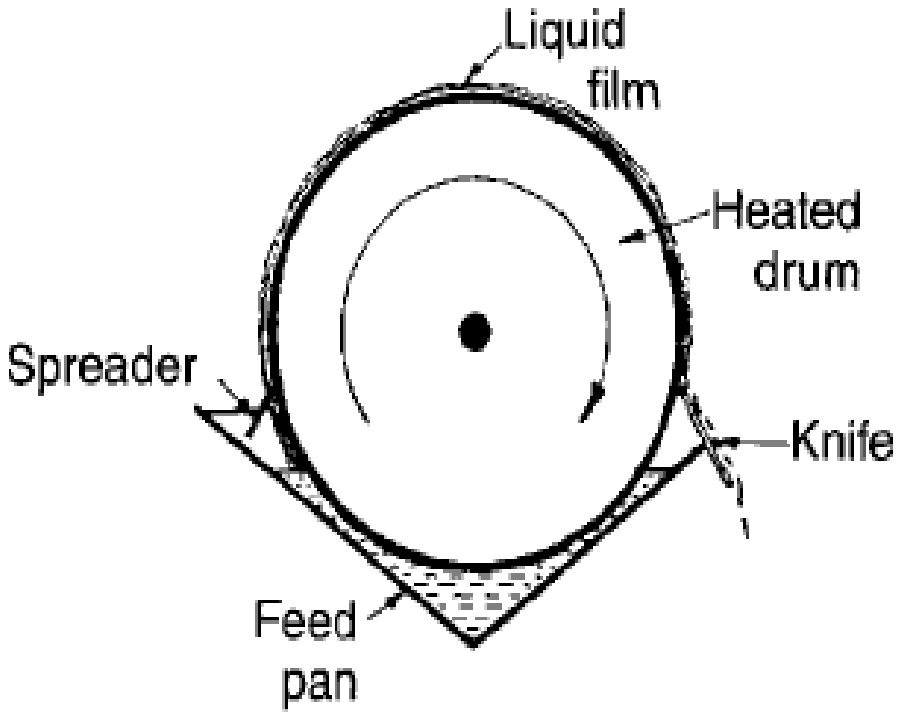
- Objectives:
  - To spread the liquid to a large surface area for heat and mass transfer
  - To provide an effective means of collecting the dry solid

...

- Two main types are used:
  - The first spreading the liquid to a thin film on to a drum
  - The second dispersing the liquid to a spray of small droplets

...

- Drum drier (film dryer)
  - The drum dryer consists of a drum, 0.75 - 1.5 m in diameter which heated internally, usually by steam and rotate on its longitudinal axis
  - The liquid is applied to the surface and spread to a film
  - The product is scraped from the surface of drum by means of knife


Liquid
film
Heated
drum
Spreader
Knife
Feed
pan

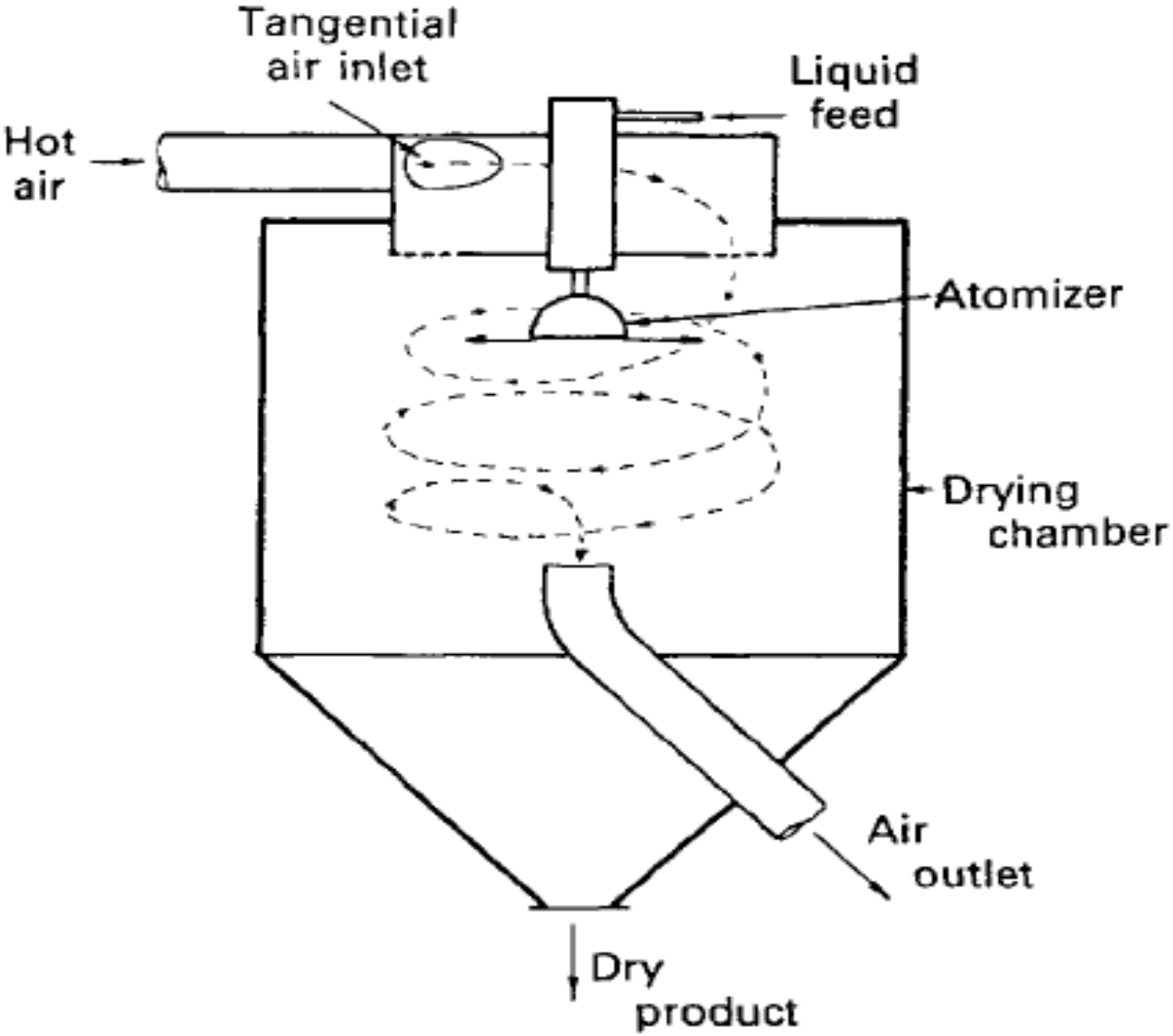
- Advantages of the drum drier
  - The method gives rapid drying
  - The equipment is compact, occupying much less space than the spray-drier
  - Heating time is short, being only a few seconds
  - The drum can be enclosed in a vacuum jacket, enabling the temperature of drying to be reduced
  - The product is obtained in flake form

...

- The only disadvantage is that operating conditions are critical and it is necessary to impose careful control on feed rate, film thickness, speed of drum rotation and drum temperature.

...

- Spray dryer
  - Provides a large surface area for heat and mass transfer by atomizing the liquid to small droplets
  - The droplets are sprayed into a stream of hot air so that each droplet dries to solid particles
  - The sprays are produced by either rotary or nozzle atomizer


Tangential
air inlet
Liquid
feed
Hot
air
Atomizer
Drying
chamber
Air
outlet
Dry
product

...

- The character of the particles is controlled by the droplet size,
- Jet atomizers are easily blocked by rapid evaporation and deposition of solid on the nozzle, and the droplet size is likely to vary
  - This is not the case with rotary types of atomizer
- Spray-dried products are easily recognizable, being uniform in appearance.
- The particles have a characteristic shape, in the form of hollow spheres sometimes with a small hole

...

- Advantages of the spray drying process
  - Millions of small droplets give a large SA for heat and mass transfer
  - the droplets do not attain a high temperature
  - The characteristic particle form gives the product rapid dissolution
  - The resulting powder will have a uniform and controllable particle size.
  - The product is free flowing, with almost spherical particles
  - Labor costs are low

- Disadvantages of the spray drying process
  - The equipment is very bulky, and with the ancillary equipment is expensive
  - The overall thermal efficiency is rather low

- Freeze-drying
  - Lyophilisation or cryodesiccation or drying by sublimation
  - Involves freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime
  - The theory and practice of freeze drying is based on an understanding and application of the phase diagram for the water system

- Application of the phase diagram of water to freeze drying
- the solution must be cooled to well below the normal freezing temperature for pure water
  - b/c of the depression of the freezing point caused by the presence of dissolved solutes
- It is usual to work in the range -10 to -30°C

- Sublimation can only occur at the frozen surface and is a slow process
  - The SA must be increased and the liquid thickness prior to freezing be reduced in order to reduce the thickness of ice to be sublimated
- At low pressures large volumes of water vapor are produced which must be rapidly removed to prevent the pressure rising above the triple point pressure

- Freeze drying equipment
  - Freeze dryers are composed of four basic components:

1. Chamber for vacuum drying
   - Continuous or batch operation
2. Vacuum source
   - Vacuum achieved by pumps, steam ejectors

3. Heat source
    - Heat provided by conduction or radiation
4. Vapor removal system
    - Condensers, desiccants, pumps

...

- Stages of the freeze drying process
- Freezing stage
  - The liquid material is frozen before the application of vacuum to avoid frothing
  - Several methods are used to produce a large frozen surface

- Shell freezing
  - Employed for fairly large volumes
  - The bottles are rotated slowly and almost horizontally in a refrigerated bath
  - The liquid freezes in a thin shell around the inner circumference of the bottle.
  - Freezing is slow and large ice crystals form

- Vertical spin freezing
  - In vertical spin freezing the bottles are spun individually in a vertical position so that centrifugal force forms a circumferential layer of solution, which is cooled by a blast of cold air.
  - The solution supercools and freezes rapidly, with the formation of small ice crystals

- Centrifugal evaporative freezing
  - prevents foaming when a vacuum is applied
  - The vacuum causes boiling at room temperature and this removes so much latent heat that the solution cools quickly and snap freezes
  - About 20% of the water is removed prior to freeze drying and there is no need for refrigeration.
  - Ampoules are usually frozen in this way

...

- Vacuum application stage
  - The containers and the frozen material must be connected to a vacuum source sufficient to drop the pressure below the triple point and remove the large volumes of low-pressure vapour formed during drying
  - An excess vacuum is normal in practice, to ensure that the product in question is below its triple point

- Sublimation stage
  - Heat of sublimation must be supplied.
  - Under these conditions the ice slowly sublimes, leaving a porous solid which still contains about 0.5% moisture after primary drying
  - During the primary drying, the latent heat of sublimation must be provided

...

- Heat transfer is critical - insufficient heat input prolongs the process and excess heat will cause melting
  - Prefrozen bottles are placed in individually heated cylinders, or are connected to a manifold when heat can be taken from the atmosphere.
  - Shelf-frozen materials are heated from the drier shelf
  - ampoules may be left on the centrifuge head or may be placed on a manifold, but in either case heat from the atmosphere is sufficient

...

- Vapor removal
  - The vapor formed must be continually removed to avoid a pressure rise that would stop sublimation.
  - To reduce the pressure sufficiently it is necessary to use efficient vacuum pumps, usually two-stage rotary pumps on the small scale, and ejector pumps on the large scale
  - On the small scale, vapor is absorbed by a desiccant or is cooled in a small condenser with solid carbon dioxide
  - Mechanically refrigerated condensers are used on the large scale

...

- Secondary drying
  - The removal of residual moisture at the end of primary drying is performed by raising the temperature of the solid to as high as 50 or 60°C.
  - A high temperature is permissible for many materials because the small amount of moisture remaining is not sufficient to cause spoilage.

- Advantages
  - Drying takes place at very low temperatures, so that enzyme action is inhibited and chemical decomposition, particularly hydrolysis, is minimized
  - The product is light and porous
    - The porous form of the product gives ready solubility
  - Salts do not concentrate and denature proteins, as occurs with other drying methods.
  - There is little contact with air, and oxidation is minimized

...

- Disadvantages
  - The porosity, ready solubility and complete dryness yield a very hygroscopic product.
  - The process is very slow and uses complicated plant, which is very **expensive**.
  - It is limited to certain types of valuable products which cannot be dried by any other means.

...

- Uses of freeze drying
  - The method is used for products that cannot be dried by any other heat method.
  - Biological products, for example some antibiotics, blood products, vaccines, enzyme preparations and microbiological cultures

5. Filtration and Clarification